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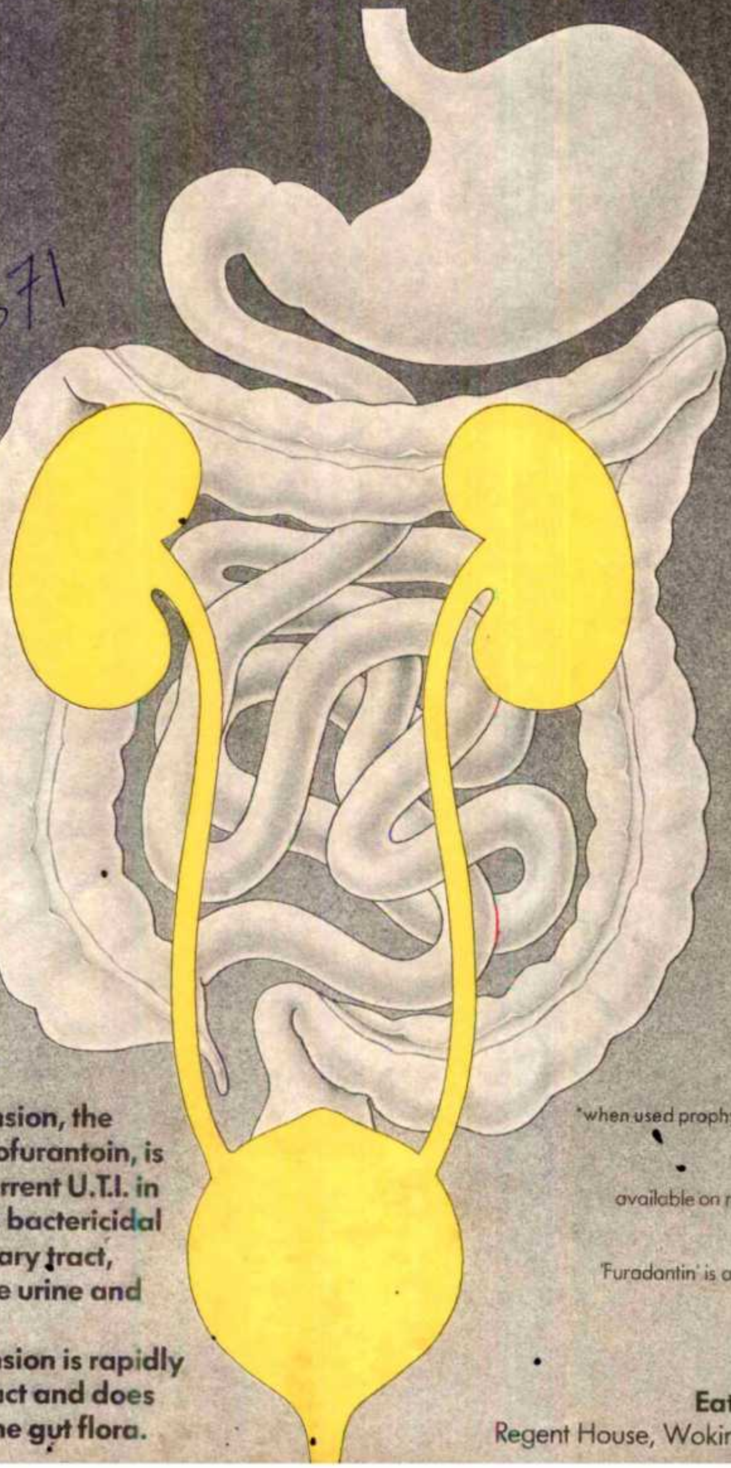

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The publication of this first issue of the 50th volume coincides with changes in both the editorial team and the style of the Journal itself. There will also be a minor change in the dates of its publication.

Professor Geoffrey Chisholm of Edinburgh has taken over from me as Editor; Mr John Newsam has succeeded Mr David Essenhigh as Assistant Editor with particular responsibilities in the editorial office, which has now been transferred to Edinburgh; and I have the difficult task of replacing Mr Innes Williams as Chairman of the Editorial Committee. We shall, however, continue to have the benefit of the advice of Mr Innes Williams and Mr Essenhigh in committee.

The changes in the front cover are mostly cosmetic; the back cover now shows the Contents; and the page range is entered on the spine. Although the primary objective in the change from single to double columns is to facilitate reading, it has the very acceptable bonus of economising on space, and so will slightly increase the contents of the Journal.

In order to publish the papers presented at the Annual Meeting of the British Association of Urological Surgeons in the same year as the meeting, these will in future appear in the December issue. Ordinary issues will be published in February, April, May, June, August and October.

These changes are, of course, simply in furtherance of the basic policy of the *British Journal of Urology*—to publish worthwhile new urological knowledge, in the most acceptable form, as quickly as is compatible with fair, careful appraisal and high quality production.

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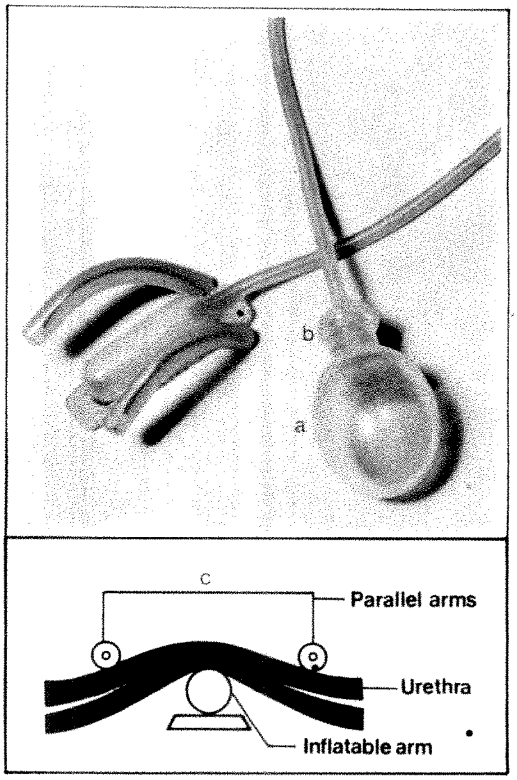

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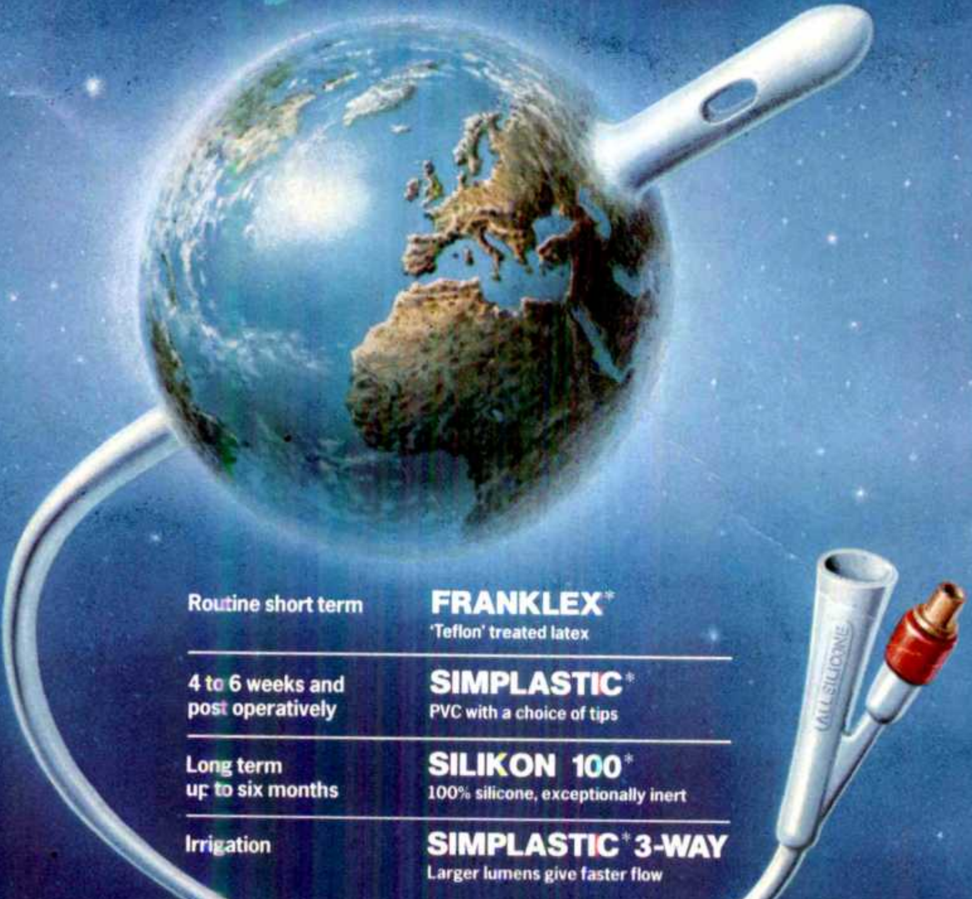

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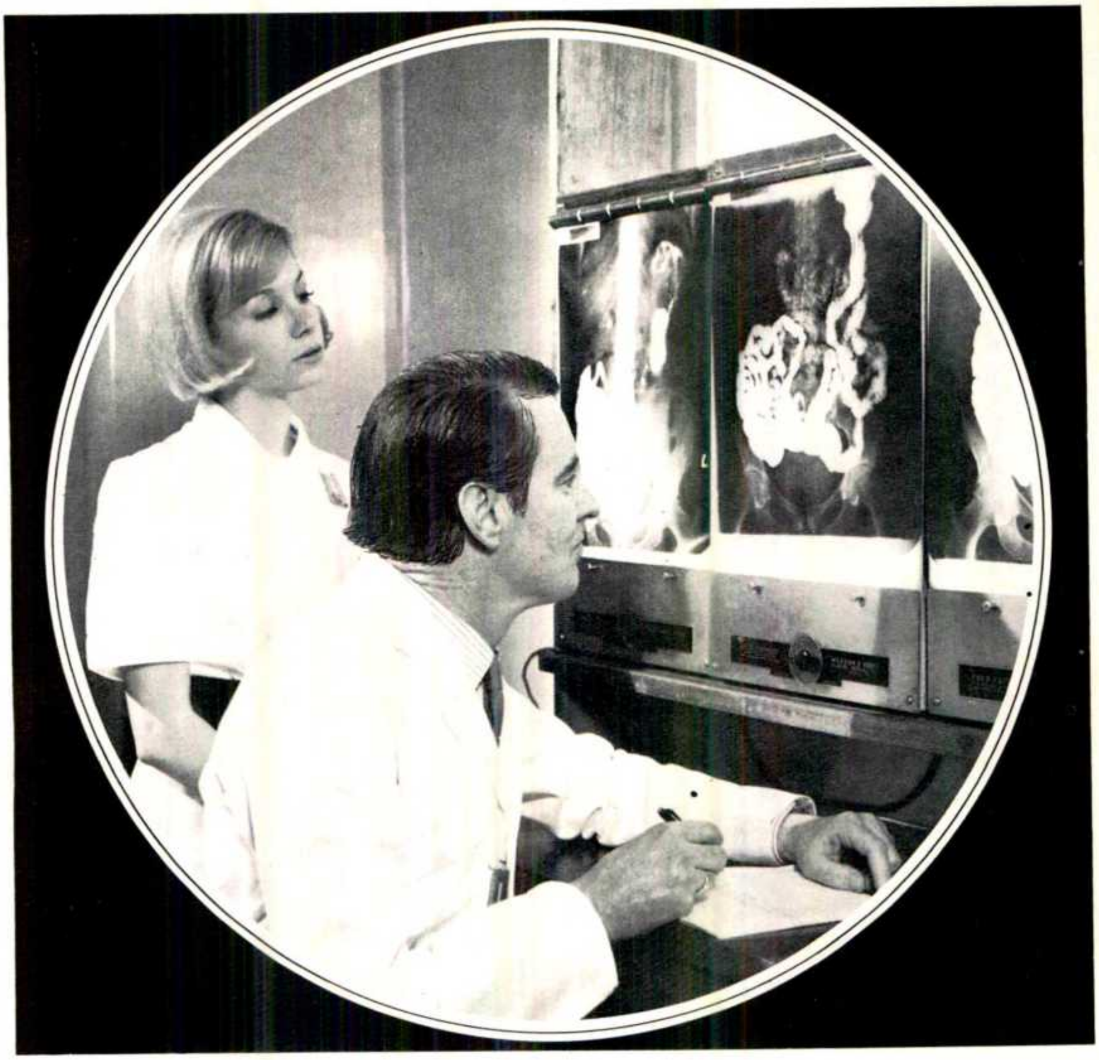

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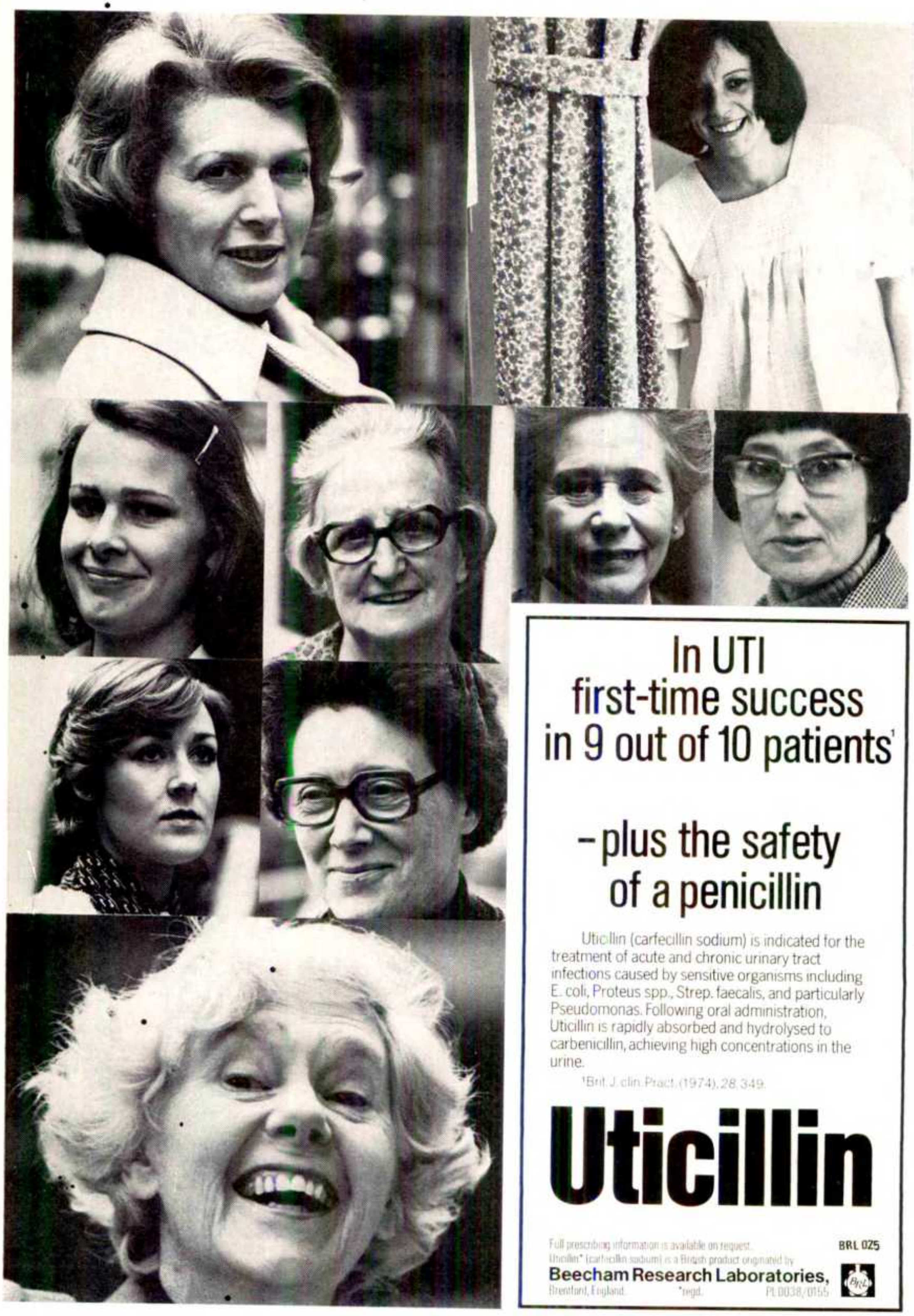

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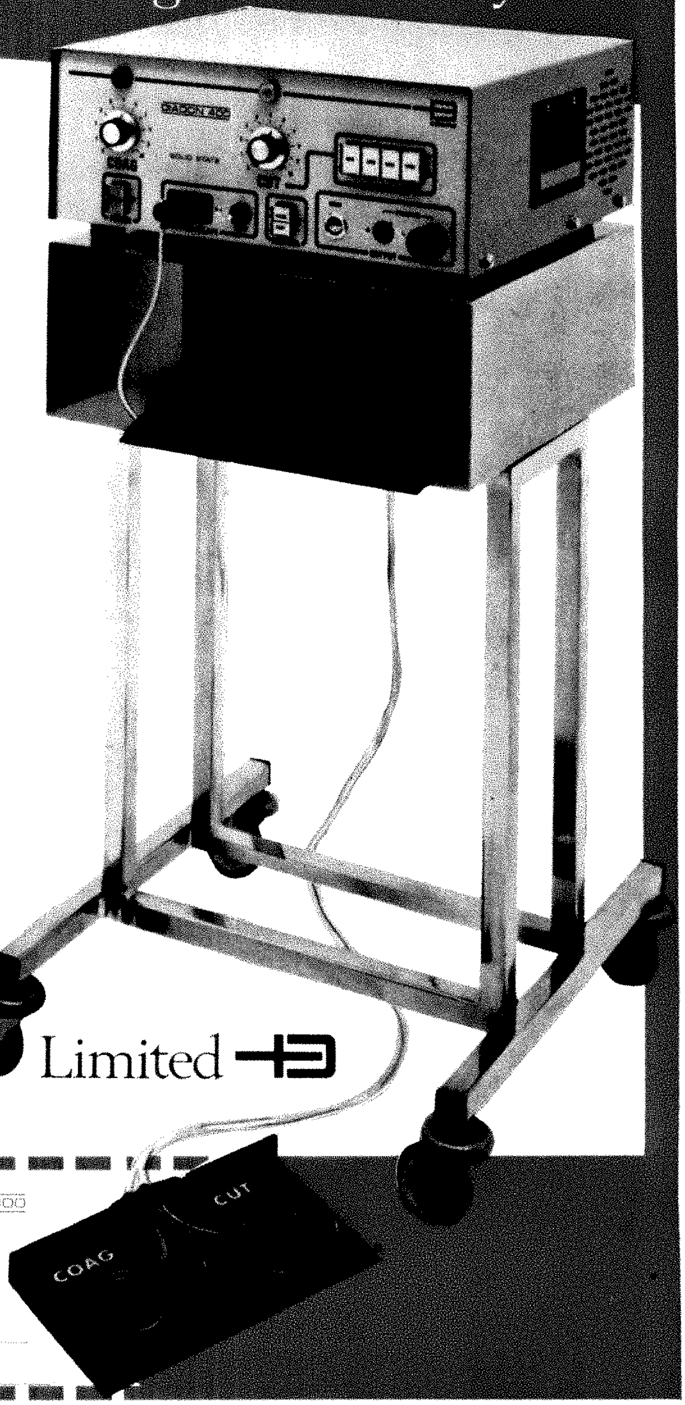

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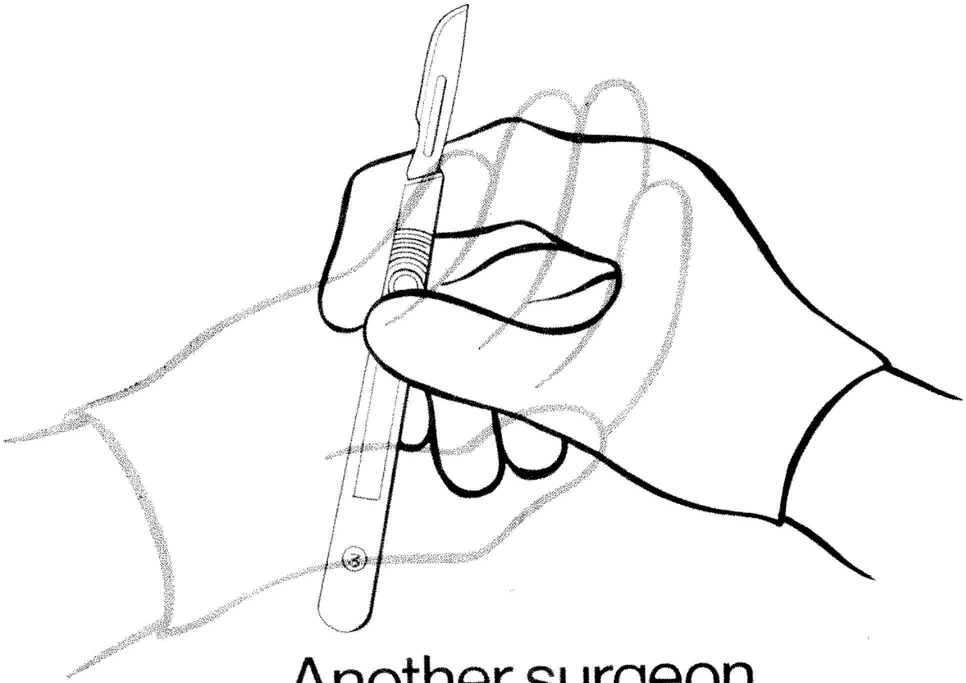

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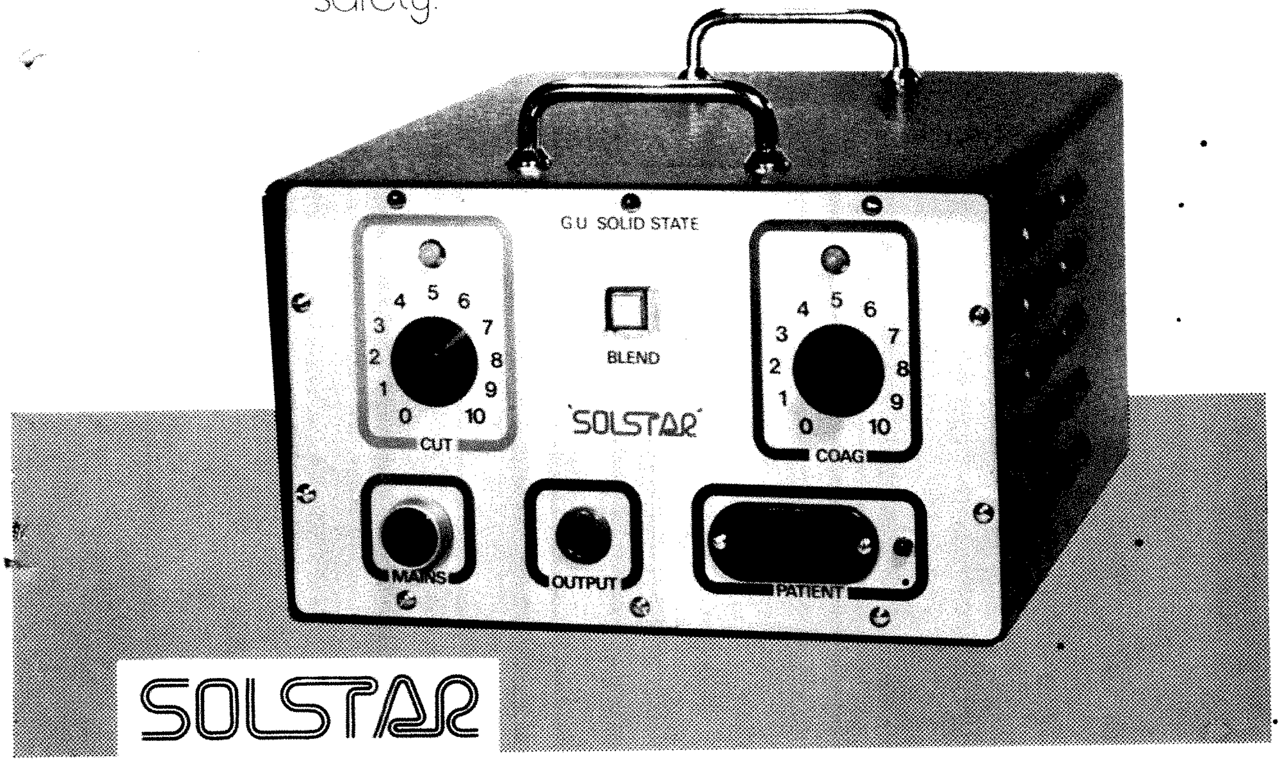

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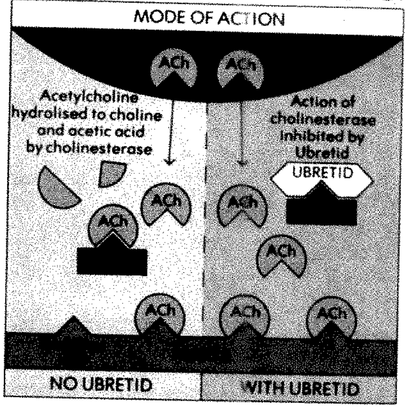
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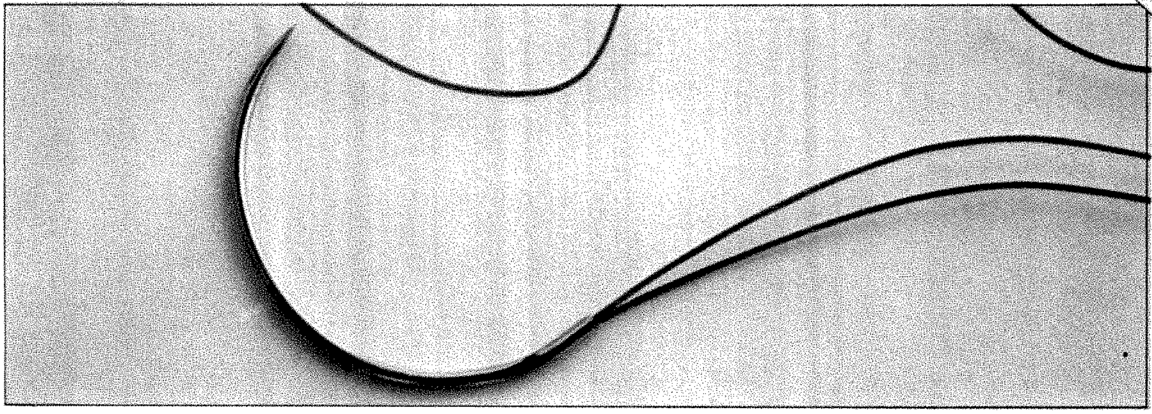

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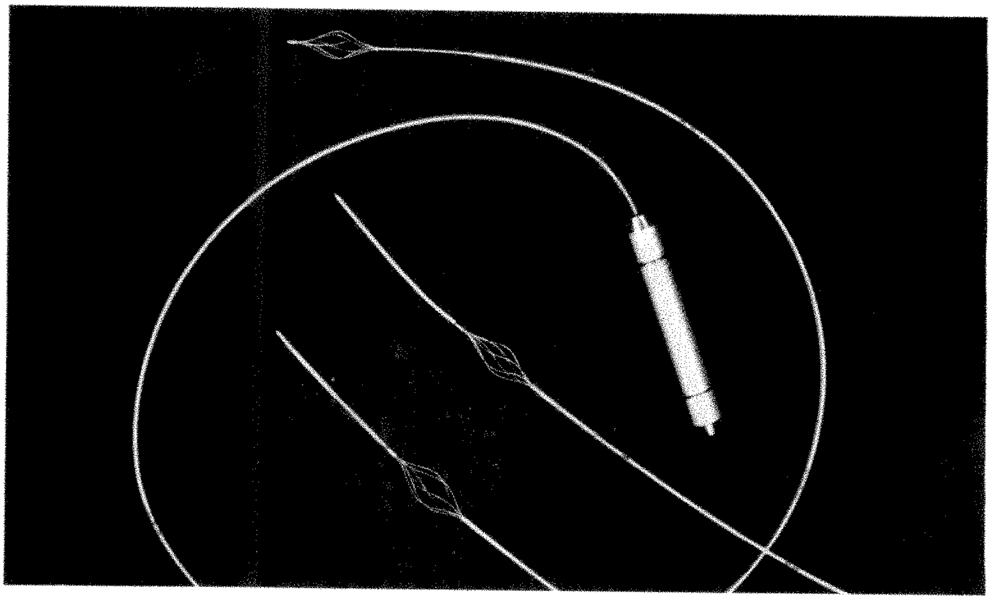

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Perfusion Characteristics of Preserved Canine Kidneys Subjected to Warm Ischaemia

V. K. MODGILL, P. A. WIGGINS and G. R. GILES

University Department of Surgery, St James's University Hospital, Leeds

Summary—Canine kidneys were subjected to 0, 15 or 30 min of warm ischaemia followed by 24 hours preservation by perfusion. Changes in perfusate concentration of acid radicles, lactate, free fatty acid and lactic dehydrogenase were assessed at 1 hour and 24 hours. With the exception of LDH concentration at 1 hour, no single parameter was capable of detecting kidneys which were so damaged as to be non-life supporting.

One major problem in cadaveric renal transplantation is the identification of irreversibly damaged kidneys by simple and reliable methods. Machine perfusion of cadaveric kidneys, apart from extending the preservation time, has a distinct advantage over simple hypothermic storage in that the "behaviour" of the kidney on perfusion can be observed prior to transplantation. Despite a grave shortage of kidneys for transplantation a significant number of organs are discarded on the basis of arbitrarily defined perfusion characteristics (Belzer, Ashby and Downes, 1968; Stephenson, Hendry and Ward, 1975) and it is not known whether they would have functioned if they had been transplanted (Shiel *et al.*, 1975). Similarly, viability studies based on morphological changes in biopsy material, enzyme release into perfusate and anaerobic metabolism within damaged kidneys are helpful but do not consistently correlate with the eventual function of the transplanted kidney (Modgill *et al.*, 1977).

The aim of this experimental study was to investigate the commonly used viability assessments in 3 groups of canine kidneys subjected to the trauma of 0, 15 or 30 min of warm ischaemia followed by 24 hours preservation and relate them to the subsequent function of these kidneys.

Methods and Materials

Female mongrel dogs weighing between 20 and 30 kg were used throughout the study. Anaesthesia was induced with sodium thiopentone (25 mg/kg) and maintained with halothane and oxygen. All the dogs had similar intravenously administered donor pre-treatment with 1 litre 5% dextrose in water, heparin 5000 units and Mannitol 12.5 g. Donor nephrectomy was carried out through a midline incision and the left kidney was mobilised with minimal handling. The ureter was divided and the renal vessels isolated. The kidney was allowed to recover from any spasm and when there was free urine flow from the cut ureter, the artery and then the vein were ligated and divided.

Those kidneys subjected to 0 warm ischaemia (Group I: 4 dogs) were immediately removed. The renal artery was cannulated and the kidney flushed with Perfudex (Pharmacia) at 8°C from a height of 100 cm till the venous effluent was clear. The kidneys were weighed and placed in standard ice containers. Those kidneys subjected to 15 min warm ischaemia (Group II: 5 dogs) and 30 min warm ischaemia (Group III: 5 dogs) after vascular isolation, were left in the peritoneal cavity for the appropriate time; the peritoneal cavity during this time was temporarily approximated with skin clips. These kidneys were similarly washed out with Perfudex, weighed and transported to the laboratory on ice.

All the kidneys were perfused in a chamber at 8°C with PPF_2 (Johnson, 1972) in a total volume of 500 ml for 24 hours. The perfusion was non-pulsatile and the flow rate was adjusted to approximately 1 ml/g/min. The pH of the perfusate was allowed to vary without adjustment. The perfusion pressure was recorded continuously by a pressure transducer and allowed to vary. After 24 hours of perfusion all kidneys were weighed and autotransplanted. The midline incision was extended and

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Accepted for publication 6 June 1977.

immediate contralateral nephrectomy carried out. The preserved kidney was transplanted in the right iliac fossa with end to end renal artery external iliac artery anastomosis; the renal vein was anastomosed end to side with the common iliac vein and the ureter was anastomosed to the bladder using a submucosal tunnel. During the anastomosis all dogs received 1 litre 4% dextrose/saline, Lasix 48 mgm and Mannitol 12.5 g.

Postoperatively all dogs were allowed free fluids for the first 24 hours and thereafter a standard meat diet. Serial estimations of serum urea and creatinine were carried out 3 times per week.

The following viability assessments were carried out:

(1) Vascular resistance expressed as mmHg/ml/min or dynes/sec/cm^5

$$R = \frac{\text{Perfusion Pressure}}{\text{Organ Flow}} \times 1333$$

(2) pH change: Prior to the introduction of the kidney into the circuit and at 1 hour and 24 hours after perfusion, the pH of the perfusate was measured using a Blood Micro System (BMS) (Radiometer, Copenhagen). The differences between the base line estimation and measurements at 1 hour and 24 hours indicated pH change during first hour and 24 hours perfusion.

(3) Perfusion lactate concentration at 1 hour and 24 hours was determined on 1 ml samples which were placed in glass tubes containing 2 ml of perchloric acid at 4°C. Lactate levels were determined using Boehringer Lactate Biochemica Test Combination Kit. Results are expressed as mg/100 ml of perfusate and also related to the weight of the kidney.

(4) Perfusate lactate dehydrogenase concentrations: Samples of perfusate were frozen at −20°C until testing. Estimations were carried out on 0.1 ml perfusate samples using the Boehringer LDH Combination Kit and results expressed as units/l and units/l/g kidney.

(5) Free fatty acids concentration was estimated in the perfusate before, 1 hour and 24 hours after perfusion using the Boehringer Biochemica Test Kit for non-esterified fatty acid and results expressed as percentage change from the base line sample.

All statistical analyses are derived from the Mann Whitney "U" Test.

Results

All the kidneys produced urine immediately after revascularisation. In Group I all the dogs survived whereas in Group II (15 min warm ischaemia) 2 dogs died in uraemia on day 3 and in Group III (30 min warm ischaemia) 4 dogs died, 3 in uraemia and 1 with pneumonia and intussusception. In this last dog the serum creatinine and urea were on the decline when death occurred.

TABLE I Post-transplant renal function serum creatinine mmol/l

Groups		*Days post-transplant serum creatinine* 3	7	21
I		N = 4	N = 4	N = 4
Nil warm ischaemia		210	100	100
		220	120	100
		230	140	100
		650	150	100
	Means	327.5	127.5	100
II		N = 5	N = 3	N = 3
15 min warm ischaemia		320	150	100
		320	210	100
		450	260	100
		600		
		685		
	Means	475	206.7	100
III		N = 5	N = 2	N = 1
30 min warm ischaemia		675	520	180
		750	550	
		850		
		900		
		727		
	Means	780	535	180

In the 3 groups of dogs, cold ischaemia prior to perfusion, the perfusion time and re-anastomosis times are similar and not statistically significant. Table I shows the serum creatinine levels on the 3rd, 7th and 21st post-transplant day in surviving animals. It can be seen that the period of warm ischaemia is directly related to the serum creatinine and thus the degree of renal injury. Similarly the rate of recovery to normal serum creatinine values is greater with kidneys which were not subjected to warm ischaemic injury.

Viability Assessments

pH change 1 hour and 24 hours after perfusion

For those kidneys in Group I the mean pH fall 1 hour after perfusion was 0.05 ± 0.03 and for Group II (15 min warm ischaemia) it was 0.08 ± 0.03. With Group III kidneys (30 min warm ischaemia) the mean pH fall at 1 hour was also 0.08 ± 0.03. There is clearly no statistical difference in these values between the 3 groups.

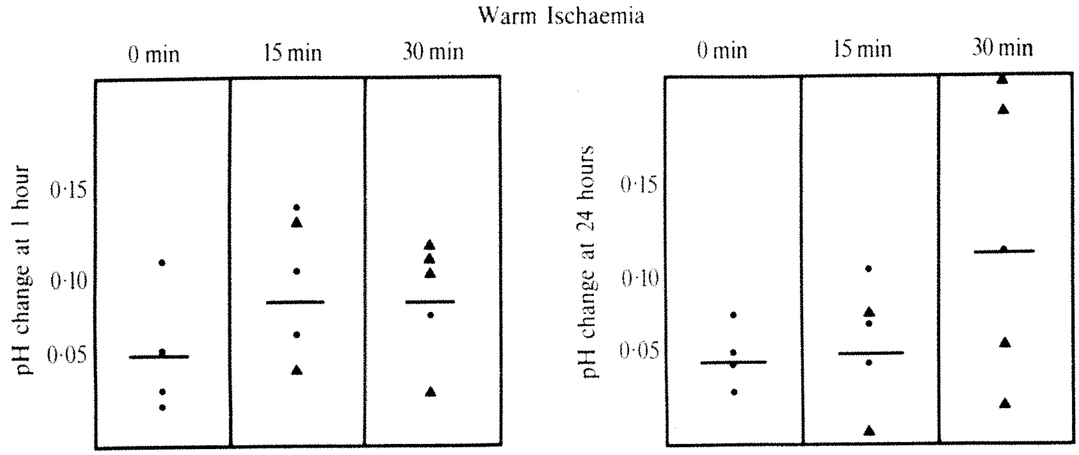

FIG. 1 Shows the change in perfusate pH after 1 hour and 24 hours of preservation. Closed circles indicate survival of animals and the closed triangles are those animals dying.

Furthermore, with 24 hours perfusion the pH fall in the perfusate in the 3 groups (0.04 ± 0.01; 0.05 ± 0.03; 0.11 ± 0.07 respectively) was not statistically significant nor was there any difference between the kidneys that functioned with survival and those that failed to function sufficiently well (p = >0.1) (Fig. 1).

Lactate concentration in the perfusate 1 hour and 24 hours after perfusion

The lactate concentration in the perfusate at 1 hour in Group I kidneys was 12.45 ± 1.64 mg/100 ml perfusate or 0.19 ± 0.03 mg/100 ml/g kidney weight. In Group II kidneys the concentration at 1 hour was 5.65 ± 3.47 mg/100 ml perfusate or 0.70 ± 0.04 mg/100 ml/g kidney weight and in Group III it was 4.7 mg/100 ml perfusate or 0.08 ± 0.03 mg/100 ml/g kidney weight.

The differences in Groups I and II and Groups I and III are statistically significant (U max Groups I and II = 20, p = <0.01; and U max Groups I and III = 20, p = <0.01). There is, however, no difference between Groups II and III. Interestingly, the statistical difference is lost between the groups with 24 hours perfusion. In Group I at 24 hours the mean lactate values were 17.32 ± 5.80 mg/100 ml or 0.26 ± 0.07 mg/100 ml/g compared with values of 17.20 ± 9.3 mg/100 ml perfusate or 0.27 ± 0.16 mg/100 ml/g kidney weight in Group II and 12.16 ± 4.38 mg/100 ml or 0.23 ± 0.06 mg/100 ml/g in Group III (Fig. 2). Furthermore, in Groups II and III there was no significance in the lactate values at 1 hour of perfusion between the kidneys that functioned satisfactorily (4.42 ± 3.99) and those that did not (6.34 ± 2.9 mg/100 ml).

Lactic dehydrogenase release

The lactic dehydrogenase release at 1 hour perfusion in Group I was 173.5 ± 125.2 units/l or 2.49 ± 1.79 units/l/g kidney weight. In Group II it was 229 ± 322 or 3.4 ± 4.52 units/l/g and Group III it was 147 ± 85.43 units/l or 2.89 ± 1.51 units/l/g kidney weight. The differences in the groups expressed as either units/l or related to the kidney weight were not statistically significant (p = >0.1) (Fig. 3). However a discriminating fact emerged for kidneys subjected to warm ischaemia (Groups II and III) in so much that all dogs died which had received a kidney releasing sufficient LDH in to perfusate to raise it to a level greater than 100 units/l (Fig. 3).

With 24 hours perfusion, the lactic dehydrogenase concentrations increased in all the groups. In Group I the LDH concentration was 293.3 ± 144.7 u/l or 4.42 ± 1.98 u/l/g; in Group II 888.6 ± 579.5 u/l or 13.89 ± 9.5 u/l/g and in Group III it was 1046.8 ± 902.1 u/l or 19.6 ± 15.8 u/l/g kidney weight. This now assumes statistical significance between Groups I and II (U max = 19, p = <0.025) and between Groups I and III (U max = 20, p = <0.01) whereas there is no difference between Groups II and III (p = >0.2). There is no longer a discriminating level of LDH concentration in the perfusate which will detect a severely damaged kidney (Fig. 3).

Perfusion characteristics at 1 hour and 24 hours of perfusion

The mean flow at 1 hour in Groups I, II and III was 1.0 ± 0.02 ml/min, 0.80 ± 0.36 ml/min and

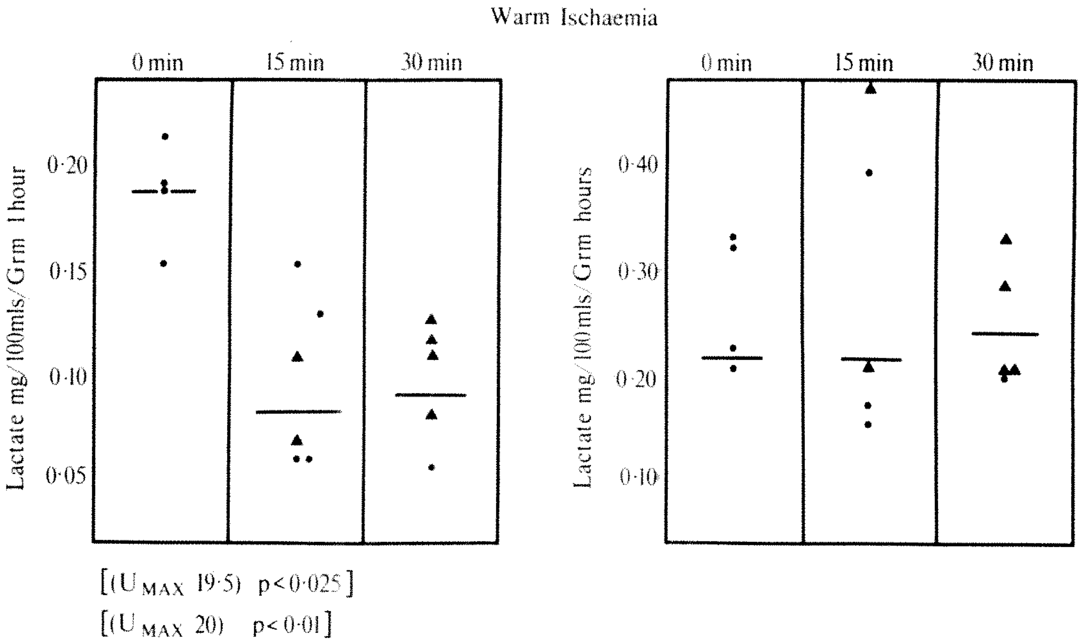

FIG. 2 Shows the perfusate lactate concentration per g of kidney after 1 hour and 24 hours of preservation in the 3 groups of dogs. Closed triangles indicate dogs dying after transplantation.

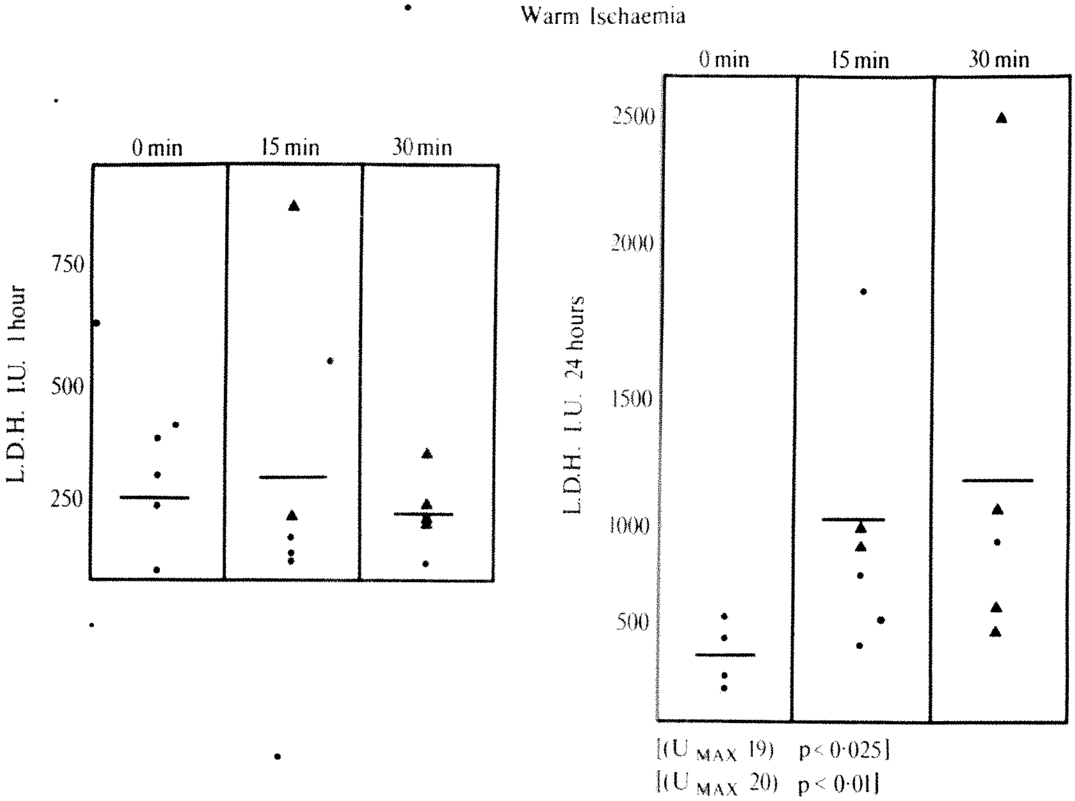

FIG. 3 Shows the lactic dehydrogenase level in the perfusate of the 3 groups of experiments at 1 hour and 24 hours of preservation. Closed triangles indicate animals dying after transplantation.

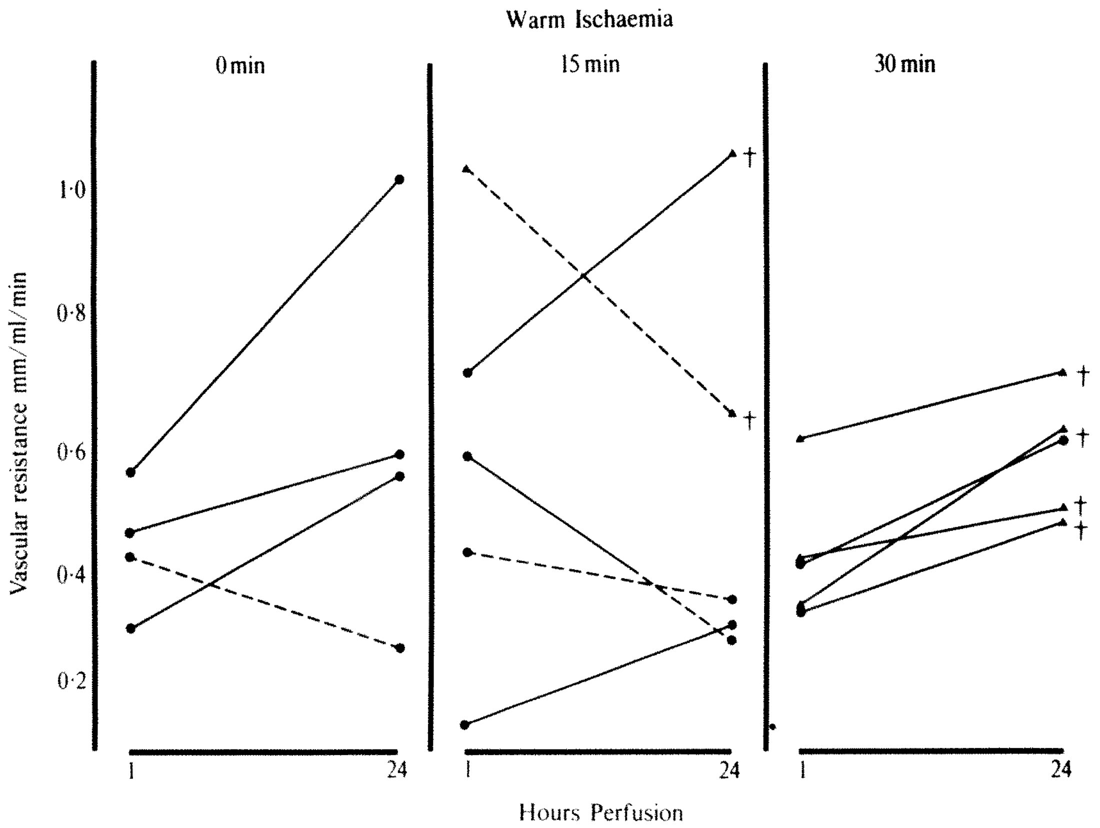

FIG. 4 Shows the vascular resistance change over 24 hours of perfusion in the 3 groups of dogs.

0.95 ± 0.11 ml/min respectively. There is clearly no statistical difference in these values.

Expressing perfusion in terms of vascular resistance the mean resistance at 1 hour in Group I was 0.59 ± 0.27 mm/ml/g or 795.07 ± 363.2 dynes/sec/cm^5, in Group II 0.57 ± 0.37 mm/ml/g or 758.76 ± 502.9 dynes/sec/cm^5 and in Group III it was 0.58 ± 0.09 mm/ml/g or 773.6 ± 120.2 dynes/sec/cm^5. 1 kidney in Group I and 3 kidneys in Group II exhibited a fall in the vascular resistance with 24 hours perfusion but all kidneys in Group III had measurable increases in vascular resistance (Fig. 4).

Free fatty acid change at 1 hour and 24 hours after perfusion

In Group I kidneys at 1 hour, utilisation of free fatty acids from the perfusate occurred in 2 kidneys (both 41% reduction) whereas in the other 2 kidneys there was non-utilisation or release of fatty acids from kidneys (39 and 34% increase in FFA levels). Similarly in Group II only 1 kidney utilised FFA and in Group III 2 out of 5 kidneys lowered the FFA in the perfusate at 1 hour.

Discussion

The identification of irreversibly damaged donor kidneys remains a major problem in renal transplantation. The development of perfusion techniques for kidney preservation has made it possible to assess the viability of donor kidneys prior to transplantation. It has been shown that warm ischaemia to the donor kidneys leads to vascular endothelial damage and to spasm of cortical vessels. Perfusion of such kidneys is followed by leakage of perfusion fluid from the vascular spaces which leads to oedema and a consequent rise in vascular resistance. Thus it has been stated that a rising perfusion pressure is usually associated with poor or non-function of the grafted donor kidney (Belzer *et al.*, 1968; Stephenson *et al.*, 1975 and Johnson *et al.*, 1973). In these experiments we have found that there was an overall rise in the vascular resistance in the 3 groups of kidneys after 24 hours preservation though it was more consistently seen in the 5 kidneys subjected to 30 min warm ischaemia. In practice, a rising perfusion pressure or conversely, a falling perfusion pressure, was not invariably associated with non-function or immediate function of the transplanted kidney. Measurement of vascular resistance *per se* was not helpful in predicting the eventual function of the autotransplanted canine kidneys.

Both warm and cold ischaemic periods in the donor kidneys result in anaerobic metabolism with an increased production of lactic acid (Chambers and Chambers, 1961) and a progressive fall in cellular pH. In some studies the accumulation of lactate in the perfusate has been well correlated with the extent of anoxic injury sustained by the donor kidneys (Baxby *et al.*, 1974). In our experiments the perfusate lactate levels failed to predict the outcome of an autotransplanted canine kidney. Paradoxically it was found that at 1 hour of perfusion the lactate levels in Group I dogs (no warm ischaemia) were significantly higher than in those kidneys subjected to warm ischaemia. However there was no further increase in the lactate levels in Group I kidneys over 24 hours whereas there were significant rises in the perfusate levels of Groups II and III kidneys. The fall in perfusate pH presumably reflects an increase in acid metabolites within the perfused organ and their continuous production within the kidney. Unlike Johnson *et al.* (1972) who were investigating canine kidneys with 60 min of warm ischaemia, we did not show a strong association between the fall in pH and the subsequent function of the transplanted kidney. Further falls in pH during the 24 hours of perfusion were small and reflect the buffering power of the perfusate.

There are difficulties with the study of metabolic processes in a preserved organ which are related to the low temperature at which metabolism must take place. It has been suggested that the substrate used by a cold preserved organ is largely in the lipid form (Krebs, 1970). The estimation of non-esterified fatty acids in the perfusate may measure in an extremely crude fashion the ability of the preserved organ to utilise this substrate. In this study there did not seem to be any form of change in perfusate FFA which obviously related either to the degree of ischaemic damage or to the subsequent function of autotransplanted kidneys. However, other workers have been able to show that increased levels of lipid within the perfusate will reduce cell breakdown and lipid release (Huang, Downes and Belzer, 1971) and Abouna (1974) was able to correlate transplant function with lipid utilisation.

The release of lactic dehydrogenase into the perfusate presumably reflects gross cell damage within the preserved organ. This parameter as an index of organ viability has been investigated by a number of authors (Belzer *et al.*, 1968; Kohn and Ross, 1971; and Hardie, Clunie and Collins, 1973) and it has been suggested that there is a linear relationship between an increase in LDH release and increasing periods of warm ischaemia. However, Johnson *et al.* (1973) investigated the washout from human kidneys and found a considerable overlap between LDH values from damaged and undamaged kidneys. These authors thought the test to be of limited value in predicting organ viability. Our own study of 32 human kidneys (Modgill *et al.*, 1977) would suggest that LDH release after 1 hour of perfusion was the most helpful parameter in the viability assessment but did not conclusively detect the irreversibly damaged organ. In this canine study, canine kidneys which had been subjected to warm ischaemia did allow a correlation between those kidneys which had life supporting function and values of LDH in the perfusate of less than 100 units/l. Continuing perfusion for 24 hours showed further increases in LDH concentration which presumably reflect continuing cell damage and although the perfusate LDH levels at 24 hours lose their discriminating value in terms of detecting irreversibly damaged kidneys, there is still a clear correlation between ischaemic damage and LDH release by the kidney.

One surprising finding in this study was the relatively high level of perfusate lactate levels at 1 hour in kidneys without warm ischaemia. Our interpretation is that perfusion in these kidneys was complete and the washout from the organ represented anaerobic glycolysis throughout the whole organ. Spasm of the intrarenal vessel and shunting is known to occur with ischaemic damage (Belzer and Kountz, 1970; Miller, Alexander and Nathan, 1972) and the lower levels of lactate concentration may reflect a failure to perfuse all areas of the kidney. This factor alone may invalidate the washout procedure as a viability index. As perfusion continues there is often evidence of a rising perfusion pressure which probably indicates increasing difficulty in perfusing the whole kidney. A rising value in the lactate or LDH level under these circumstances may reflect severe damage within a relatively small volume of perfused tissue and has, in our view, considerable prognostic significance. Conversely, we have observed large rises in perfusate LDH and lactate level after 24 hours in organs where the vascular resistance has fallen. We correlate the satisfactory result after transplant in these instances with an opening of the intrarenal vessels and improved perfusion of the whole renal tissue. This observation should encourage the use of α-blocker adrenergic agents such as phentolamine in the management of the kidney on perfusion.

This study has demonstrated again that it is difficult to correlate simple perfusate change with subsequent viability after 24 hours of perfusion. It seems probable that one of the main problems in this area is a failure to ensure perfusion of the organ in entirety and thus allow the total anaerobic metabolism and cell lysis to reflect the change of perfusate composition.

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Control of Bleeding after Renal Biopsy with Epsilon-amino-caproic acid

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Summary—EACA proved useful in controlling severe bleeding after renal biopsy. In 6 patients who required transfusion for prolonged or severe bleeding, haemorrhage ceased and no further transfusions were necessary after EACA therapy. No serious side-effects were encountered.

Urokinase, the urinary fibrinolytic activator, may prevent formation of an adequate clot after trauma to the urinary tract, thereby promoting prolonged or recurrent bleeding (McNicol *et al.*, 1961). Epsilon-amino-caproic-acid (EACA), which inhibits urokinase, has been used successfully in the treatment of bleeding after prostatectomy (McNicol *et al.*, 1961; Kirkman, 1967), and of haematuria in patients with haemophilia (Prentice *et al.*, 1971) and sickle cell disease (Vega, Shanberg and Malloy, 1971). More recently, EACA has also been recommended for treatment of prolonged haematuria following renal biopsy (Haygood *et al.*, 1971; Silverberg *et al.*, 1974). We report our experience with its use in 6 patients in whom severe or persistent bleeding occurred after percutaneous biopsy of the kidney.

Patients

During a 3-year period, 6 patients had a bleeding complication after percutaneous renal biopsy and required transfusion and surgical consultation. 3 patients had persistent gross haematuria and 3 perirenal bleeding confined to the retroperitoneal space. Because of severe or prolonged bleeding, each was treated with EACA. The clinical data and details of treatment with EACA are listed in Table I.

Routine clotting tests including thrombotest, bleeding time (Ivy) and platelet count were normal in all patients prior to biopsy. 4 patients (patients 3 to 6) were hypertensive but satisfactorily controlled and 2 (patients 5 and 6) had advanced renal failure at the time of biopsy.

1 patient (patient 5) required treatment 5 hours after biopsy because of a massive peri-renal haemorrhage with life-threatening hypotension; the average time interval between biopsy and initiation of EACA treatment in the others was 14.2 days.

The average dose of EACA employed was 9.6 g/day, and the mean duration of treatment 17.3 days. No patient required further blood transfusion subsequent to treatment with EACA. The only serious side-effect encountered was the formation of persistent clots in the bladder and ureter of patient 3, which were successfully treated by ureteric catheterisation and irrigation.

2 of the 6 cases are described in detail.

Patient 1

This young man was admitted with fever, loin pain, proteinuria and microscopic haematuria 2 weeks after an episode of acute bronchitis. Excretory urogram was normal, both kidneys measuring 14 cm in length. The tissue obtained by right renal biopsy showed juxta medullary cortex with 2 normal glomeruli and an interstitial inflammatory infiltrate, part of an artery, and the wall of a calyx. His subsequent course is outlined in Figure 1.

2 hours after biopsy the patient had heavy haematuria,

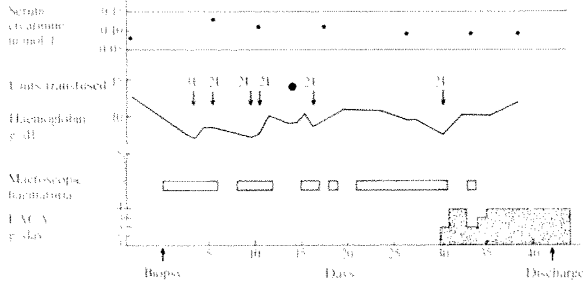

FIG. 1 Postbiopsy course of patient 1.

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TABLE 1 Relevant clinical data of patients treated with EACA

	Age	*Sex*	*Diagnosis*	*BP pre-biopsy mmHg*	*Serum creatinine (mmol/l)*		*Transfusion (units) before EACA*	*Time interval biopsy-commencement EACA (days)*	*EACA initial dose (g)*	*EACA average daily dose (g)*	*Duration of treatment (days)*	*Complications*
					pre-biopsy	*pre-EACA*						
(a) Gross Haematuria												
1.	21	M	Acute interstitial nephritis	140/85	0.08	0.09	13	31	—	3.4	46	Nil
2.	45	F	Focal glomerulonephritis due to lupus	120/80	0.12	0.20	3	8	—	12.4	5	Nausea
3.	30	M	Hypertensive nephrosclerosis	140/80	0.21	0.27	2	9	5	9.0	13	Persistent clots in urinary tract
(b) Perirenal Haematoma												
4.	30	F	Hypertensive nephrosclerosis	130/80	0.10	0.15	3	8	5	6.9	21	Nil
5.	55	M	"End-stage" renal disease	150/90	1.58	1.16	5	15	—	9.7	14	Nil
6.	54	M	"End-stage" renal disease	160/80	0.83	0.83	3	5 hours	—	16.0	5	Nil

which continued with the appearance of clots. On day 6 the serum creatinine had risen to 0.13 mmol/l. Excretion urography showed that the right kidney had reduced uptake and excretion of contrast material. The haematuria ceased the next day but recurred accompanied by shock (blood pressure 60/0 mmHg) 2 days later. At cystoscopy on day 11 a litre of thick clot was washed from the bladder; old clot was seen issuing from the right ureteric orifice, but a right ureteric catheter was passed to 25 cm without obstruction. Again the haematuria cleared, only to recommence on day 15. On days 19 and 28 technetium-99 renal scans showed a progressive diminution of uptake by the right kidney.

By day 31 the patient had received 13 units of blood. EACA was commenced in a dosage of 1 g orally every 6 hours. Fresh haematuria ceased that day, although some old clots appeared in the urine 3 days later. The haemoglobin level rose spontaneously, and no further transfusions were necessary. The serum creatinine remained unchanged at 0.09 mmol/l following the administration of EACA.

The patient was discharged 42 days after biopsy, but the EACA was continued at a daily dosage of 4 g for 3 weeks, then 2 g for 2 weeks. An excretion urogram performed 10 weeks after biopsy showed that the right kidney was now smaller than the left (12.6 cm compared to 14.7 cm) and concentrated the dye less well. The right renal outline was regular, and calyces, pelvis and ureter appeared normal. 1 year later, he remained normotensive (100/60 mmHg) and his renal function was unchanged (serum creatinine 0.09 mmol/l), although there had been further shrinkage of the right kidney to 10 cm.

Patient 4

A 30-year-old woman undergoing investigation for hypertension and microscopic haematuria, underwent right renal biopsy. The principal findings were of hypertension, with advanced arteriolar changes and an interstitial reaction.

She was discharged from hospital the day after biopsy but 8 days later was readmitted with shock (blood pressure 40/0 mmHg) and a large tender mass in the right flank. An intravenous urogram showed markedly diminished function of the right kidney (Fig. 2a). The haemoglobin level was 10.0 g/dl compared to 15.2 g/dl at the time of biopsy, and the serum creatinine had risen from 0.10 to 0.15 mmol/l.

3 units of blood were given within 24 hours and EACA was commenced intravenously—5 g statim followed by 1 g 6-hourly. The next day blood pressure (170/100 mmHg) and tissue perfusion had been restored, the haemoglobin level was 10.8 g/dl and the serum creatinine 0.12 mmol/l. No further blood transfusion was required.

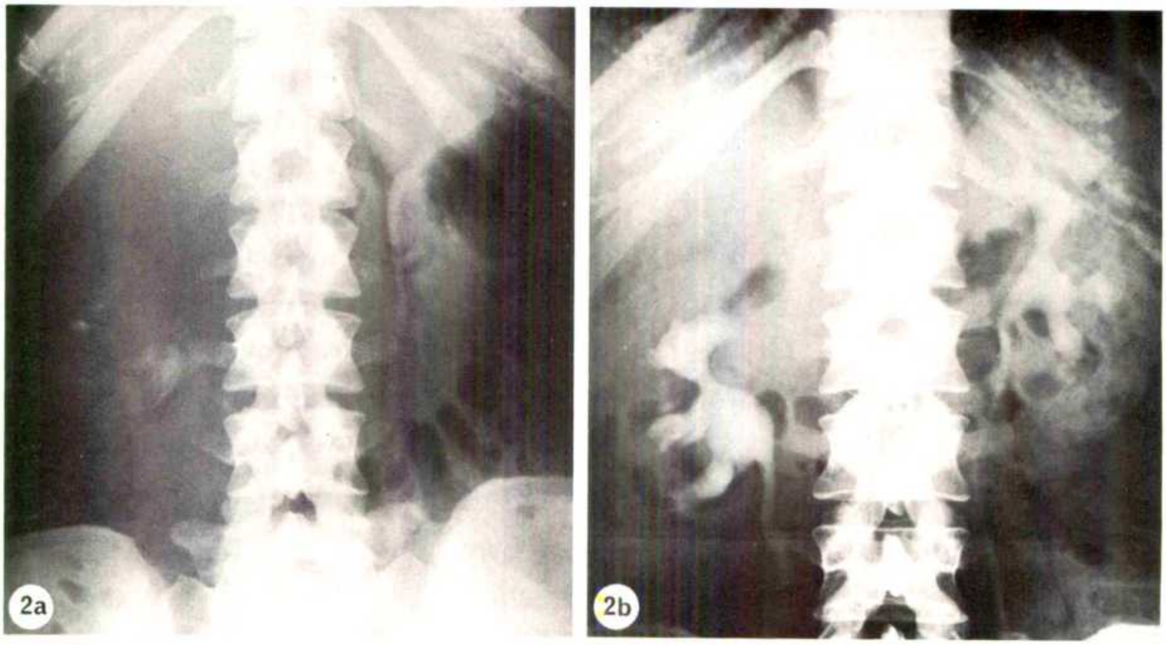

FIG. 2 Excretory urograms in patient 4: (a) 8 days after right renal biopsy, showing poor excretion on that side, and (b) 45 days after biopsy and following treatment with EACA, showing equal dye excretion on both sides.

At the end of 21 days' therapy with EACA the haemoglobin level was 12.1 mg/dl and the creatinine 0,11 mmol/l. 45 days after biopsy an excretory urogram showed equal concentration and excretion of dye by both kidneys (Fig. 2b).

Discussion

Although severe bleeding after percutaneous renal biopsy is uncommon, it is significantly increased in the presence of hypertension or renal impairment (Diaz-Buxo and Donadio, 1975). 4 of the 6 patients in the current series were hypertensive, but in none of these was biopsy undertaken until satisfactory blood pressure control had been achieved by drugs. 2 of the 6 had advanced renal impairment and although some groups have advocated that such patients should not undergo biopsy, the value of tissue diagnosis has been documented (Curtis *et al.*, 1976). Moreover, the recognition that several forms of glomerulonephritis are prone to recur in kidney grafts (McPhaul *et al.*, 1976) has stressed the importance of obtaining a precise diagnosis in all patients with renal failure who are candidates for transplantation.

Prolonged haematuria following biopsy does not usually require operative intervention (Kark *et al.*, 1958; Muth, 1965) but when the bleeding is peri-renal, exploration and/or nephrectomy is more likely (Slotkin and Madsen, 1962). EACA has been recently recommended for the control of severe bleeding after renal biopsy (Haygood *et al.*, 1971; Silverberg *et al.*, 1974).

In 5 of the 6 patients so treated in the current series there was a rapid response to EACA-therapy with cessation of bleeding. Only in patient 3 did intermittent haematuria and the passage of clots continue following EACA. However, no patient required further blood transfusions following treatment with EACA.

The recommended dose of EACA to inhibit systemic plasminogen activation is 5 g initially, followed by 1 g hourly to maintain blood levels of 13 mg/100 ml (Bergin, 1966), but because urinary concentrations of EACA are 50 to 100 times plasma concentrations (McNicol *et al.*, 1961) a smaller dosage suffices, especially when the problem is purely that of haematuria. In our series the daily dose given, which varied from 3.4 to 16.0 g (mean 9.6 g), was adequate to control bleeding.

The more serious side-effects of EACA include glomerular capillary thrombosis (Charytan and Purtilo, 1969; Purtilo, Constantian and De Girolami, 1975) and insoluble fibrin clots in the urinary tract (Coggins and Allen, 1972). Most documented cases of glomerular clotting had disseminated intravascular coagulation (DIC) when given EACA, which was believed to accentuate intravascular thrombosis while inhibiting secondary fibrinolysis and the bleeding tendency (Naeye, 1962; Bergin, 1966). There was no evidence of DIC in our cases when EACA was given, and none developed evidence of glomerular capillary thrombosis.

1 patient, however, developed nausea, and in another (patient 3), the development of large clots in the urinary tract was possibly due to EACA therapy. Nevertheless, these clots were not of the insoluble fibrin type described by Coggins and Allen (1972), and that their formation was unequivocally due to EACA treatment is by no means certain; patient 1, for example, developed similar clots before treatment with EACA, and also required cystoscopic lavage.

No patient developed deterioration of renal function attributable to EACA. In patients 1 to 4 the serum creatinine levels rose after biopsy but after treatment with EACA fell to pre-biopsy levels. Patient 1 showed radiographic evidence of permanent damage to the biopsied kidney 1 year after the procedure, but this is a known sequela of renal trauma (Glenn and Harvard, 1960).

The response to therapy and absence of serious complications suggest that in selected cases of bleeding after renal biopsy, when there is no evidence of intravascular coagulation, the administration of EACA is useful in accelerating intrarenal haemostasis. It may shorten hospitalisation, and reduce the need for blood transfusions and operative intervention.

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Patient 4 was under the care of Dr Ross Jeremy, Honorary Physician at Sydney Hospital. We wish to thank him for permission to include this case in the series.

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Ultrastructure and Pathogenesis of Human Urinary Calculi

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Summary—The ultrastructure of human urinary calculi was studied using scanning and transmission electron microscopy. The hydroxyapatite constituent of the stones was often present in the form of spherical aggregates of the minute apatite crystallites (1 to 10 μ in diameter). In most cases, the spherical apatite deposits consisted of concentric lamellae of crystallites. The spherical apatite deposits, described in detail for the first time in urolithiasis, were similar to those found in a variety of calcified tissues including nephrocalcinosis and malakoplakia.

The identification of the constituents of urinary calculi often provides the basis for the clinical management of urolithiasis in recurrent stone formers, and is of the utmost importance in research dealing with urinary stone formation. In the past, chemical (Prien and Frondel, 1947; Hodgkinson, 1971), optical (Prien and Frondel, 1947), X-ray powder diffraction (Prien and Frondel, 1947; Pollack and Carlson, 1969), and infrared spectrometry (Pollack and Carlson, 1969; Takasaki, 1971) techniques have been used to identify stone constituents. While these techniques have proved invaluable in the routine analysis of stones, they have provided little insight into the ultrastructure of uroliths. A description of the morphology and relationship of the stone constituents at the ultrastructural level is of the utmost importance because of (1) the proposed role of epitaxy in stone formation (Lonsdale, 1968) and (2) the small size of the hydroxyapatite-like crystallites which are the most prevalent crystalline constituent of uroliths. Study of the hydroxyapatite-like material in urinary calculi might provide some insight into the similarity of the morphogenesis of uroliths and other types of pathological tissue calcification in which apatite is the primary constituent.

Transmission electron microscopy (TEM) has only occasionally been applied to the study of urinary calculi because of the difficulty encountered in thin sectioning the material (Meyer, Finlayson and DuBois, 1971; Boyce, 1972). Such previous studies have revealed little information about the apatite component of stones. Scanning electron microscope (SEM) techniques have only recently been utilised for the study of stone structure (Boyce, 1972). However, the most recent work indicates that SEM studies can provide unique insights into the stone morphogenesis (Spector and Jameson, 1976).

The objective of the present study was to utilise scanning and transmission electron microscope techniques to reveal the ultrastructural features of apatite deposits in urinary calculi that might provide some insight into the pathogenesis of uroliths.

Materials and Methods

Urinary calculi surgically removed from 25 patients were either allowed to air dry immediately, or were placed into 3% cacodylate-buffered gluteraldehyde by operating room personnel. In some cases, the individual stones were dissected to provide samples for SEM and TEM and for routine analysis by microradiography, polarising light microscopy, and X-ray powder diffraction.

After a minimum of 24 hours, the fixed stones were washed in cacodylate buffer and dehydrated in successive solutions of 20, 50, 75, 95, and 100% ethanol for as long as 8 hours each.

Stones or stone fragments were fractured with a sharp blade prior to examination in the SEM. Care was taken to note how the fracture surface related to the intact

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stone. Specimens in 100% ethanol were air dried. The stone specimens were examined in an SEM equipped with an energy dispersive X-ray analysis system.

Stone specimens allotted for TEM were embedded in Epon. Thin sections were prepared on an ultramicrotome equipped with a diamond knife. A variety of trough solutions including Tris and cacodylate buffers, and a saturated calcium phosphate solution were used to inhibit demineralisation during ultramicrotomy.

The identification of the crystalline constituents of the calculi was based on X-ray powder and electron diffraction and energy dispersive X-ray analysis.

Results and Discussion

The hydroxyapatite material in the uroliths was often present in the form of spherical deposits (Fig. 1a) generally measuring 1 to 10 μ in diameter in the SEM. The spheres were aggregates of individual hydroxyapatite crystallites which were a few hundred Angstroms to a few thousand Angstroms in size. These spherical apatite deposits could also be seen in ground sections of urinary calculi viewed in the light microscope (Fig. 1b). However, identification of these unusual structural features in histological preparations was generally facilitated by prior SEM study of portions of the same stones.

Closer examination of the ground sections of the calculi revealed that individual apatite deposits appeared to have grown on the surface of other spherical deposits and on adjacent calcium oxalate dihydrate crystals (Fig. 1b). This latter observation was more clearly delineated in the SEM (Fig. 1c).

The hydroxyapatite spherical deposits were revealed as a component of "secondary" magnesium ammonium phosphate stones, as well as calcium oxalate calculi. In addition, the spherical apatite aggregates found in stones that

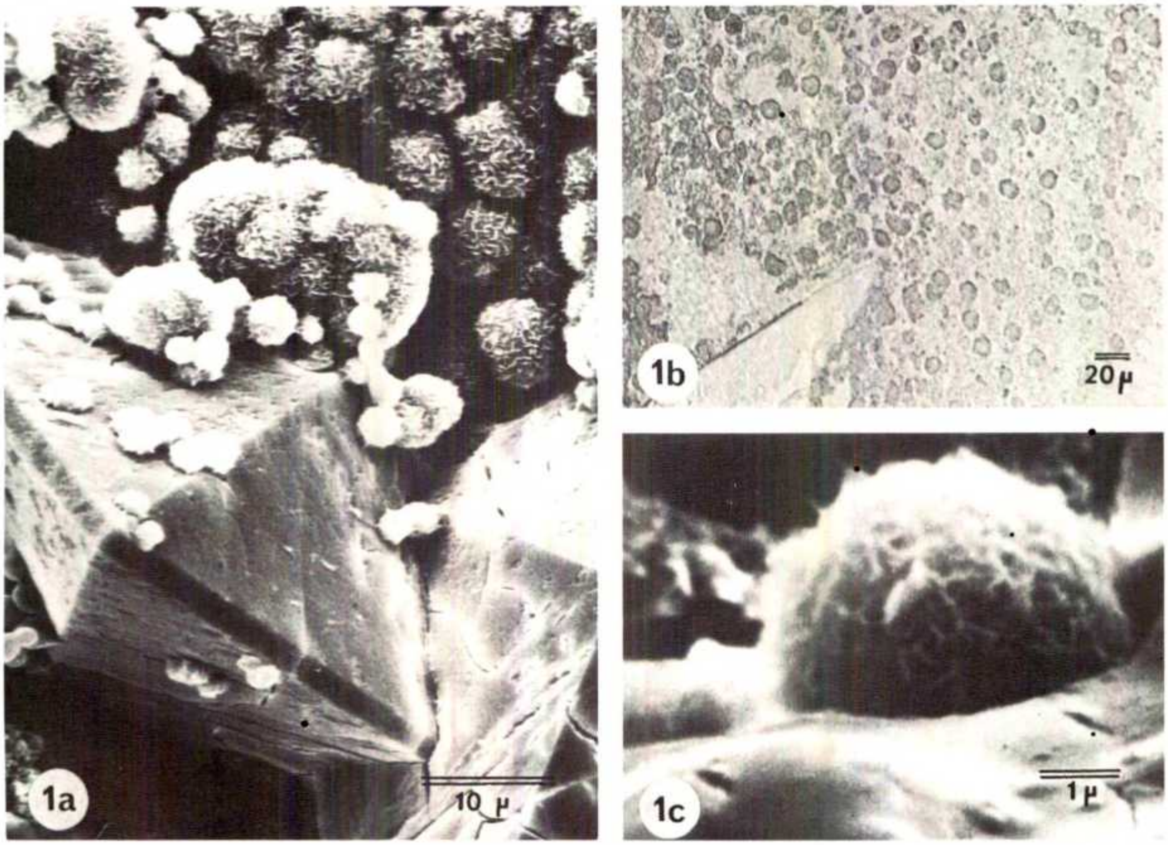
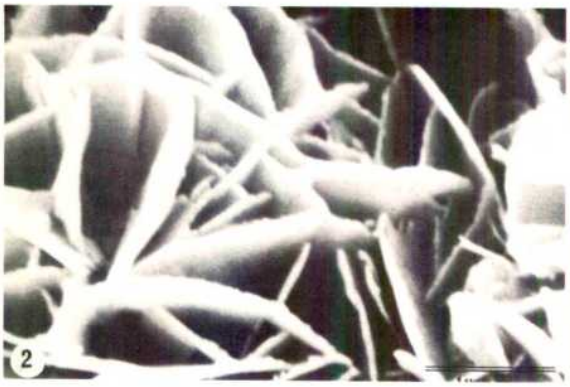
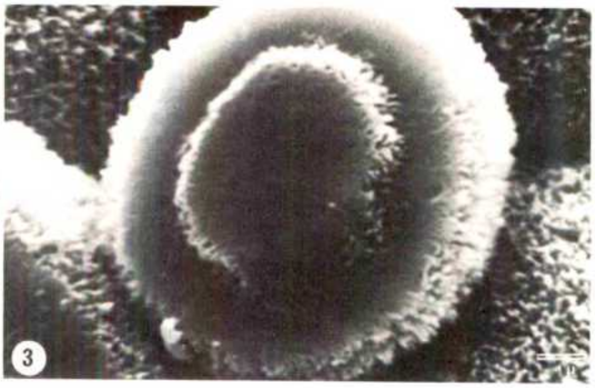


FIG. 1 (a) Scanning electron micrograph of spherical hydroxyapatite deposits in a calcium oxalate stone. The octahedral-shaped crystals are calcium oxalate dihydrate. (b) Light micrograph of an area similar to that in (a). (c) Scanning micrograph of a spherical deposit budding from the surface of a calcium oxalate dihydrate crystal. The mound-like protrusions are electron beam induced artifacts.





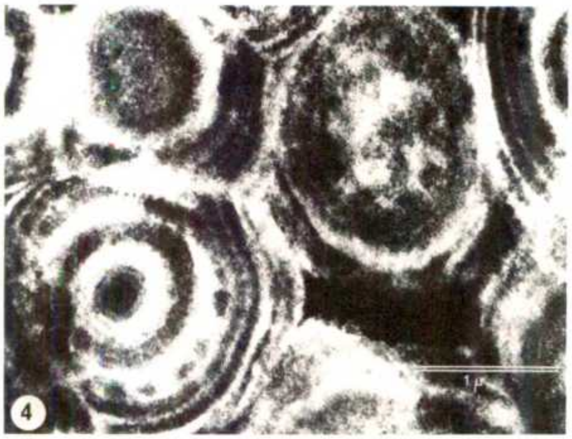


FIG. 2 Scanning micrograph of plate-like hydroxyapatite crystallites often observed on the surface of the spherical hydroxyapatite aggregates.

FIG. 3 Scanning micrograph of a fracture plane through a spherical deposit which consisted of distinct concentric lamellae. Distinct layers also coated masses of coalesced spheres.

FIG. 4 Transmission electron micrograph of the concentric spherical lamellae of apatite deposits in a human stone. The section was cut with a diamond knife using a saturated calcium phosphate trough solution to inhibit demineralisation.

were initially air dried were similar to those found in stones that were fixed and dehydrated. These deposits often accounted for large portions of the stones and were found to account for entire layers in calculi with a laminated structure.

The individual crystallites on the surface of the spheres were often plate-like, about 5000 Å long by a few hundred Angstroms in thickness (Fig. 2). These crystallites had a distinct needle-like or fibrous appearance at lower magnifications, and except for size, were very similar to bone crystallites. In some cases, the spherical deposits had a relatively smooth surface while in other cases, rod- or ribbon-like crystallites protruded from the spheres.

Fractures through the spherical deposits revealed that in some cases, the spheres consisted of several discernible concentric lamellae (Fig. 3). These distinct layers of crystallites were also observed to coat large areas of coalesced spheres and generally appeared to represent successive stages of growth of the apatite deposits.

Corresponding TEM studies also revealed the presence of hydroxyapatite in a concentric spherical lamellar structure (Fig. 4). Lamellae or rings having many apatite crystallites alternated with lamellae having few or no crystallites. The ring-like features of the apatite deposits were observed in TEM sections prepared using various ultramicrotome trough solutions. In some cases, the spherical deposits consisted of only core and surface regions which appeared to be distinguished by the size, shape, and/or orientation of the constituent crystallites.

The sphere-shaped aggregates of hydroxyapatite crystallites revealed in urinary stones in the present study should not be confused with the larger (on the order of millimetres) calcium-containing spherules described in previous studies (Boyce *et al.*, 1958). These larger spherules often contain calcium oxalate monohydrate as well as apatite. The apatite crystallites within these spherules may themselves be aggregated into the smaller concentrically laminated spherical deposits described in the present study. The small sphere-shaped structures described in the present study thus appear to be the smallest spherical subunit of aggregation of apatite crystallites in urinary stones.

The fact that these deposits have a characteristic structure and size range (about 1 to 10 μ) indicates that they are not simply a smaller form of the calcium-containing spherules noted in previous studies (Boyce *et al.*, 1958).

The small spherical hydroxyapatite deposits (1 to 10 μ in diameter) described in detail for the first time in urinary stones are strikingly similar in structure and size to the spherical hydroxyapatite deposits identified in a variety of pathological disorders including nephrocalcinosis (Haggitt and Pitcock, 1971), malakoplakia (Lambird and Yardley, 1970; Thorning and Vracko, 1975), aortic valve calcification (Kim and Huang, 1971), Sturge-Weber disease (Guseo, 1975) and many others. In each of these cases, the hydroxyapatite deposits are spherical aggregates of minute hydroxyapatite crystallites which often appear to consist of concentric lamellae.

The similarity of the apatite deposits identified in calculi and in nephrocalcinosis and malakoplakia is of particular interest. These deposits have also been identified in histiocyte-like cells in the renal cortex (in Bartter's syndrome), in the interstitium of the medulla (Haggitt and Pitcock, 1971), and in microcalculi in renal tubules (in urolithiasis). The present observations suggest that either (1) the apatitic deposits in urinary stones may be derived in part from renal calcification, or (2) the morphogenesis of apatite deposits in urine may be similar to the mechanism of formation as it occurs intra- or extracellularly. While the former implication is of obvious importance, the latter possibility suggests that the formation of these apatitic deposits in tissue does not necessarily have to be cell mediated as has been recently suggested for the pathogenesis of malakoplakia (Thorning and Vracko, 1975).

In either case, the observation that the apatite deposits in urinary calculi are morphologically similar to those in a variety of other pathological tissues should prove to be valuable for synthesizing and testing hypotheses describing the pathogenesis of urolithiasis and other calcified disorders.

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Transient Ureteric Dilatation in Neonates with Imperforate Anus: a Report of 4 cases

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Summary—In a series of 64 patients with imperforate anus, 4 were identified with ureteric dilatation without vesico-ureteric reflux. The appearance resembled that of the primary obstructive megaureter. However, since the dilatation resolved spontaneously in each case, it is concluded that the condition represents a separate entity, the cause of which has not yet been elucidated.

It is well established that all types of imperforate anus are associated with a high incidence of abnormalities of the urinary tract (Singh *et al.*, 1974; Hasse, 1976). In 3 series (Smith, 1968; Wiener and Kiesewetter, 1973; Singh *et al.*, 1974) there were examples of hydroureter without vesico-ureteric reflux. By implication this might be regarded as the same condition as primary obstructive megaureter (Williams, 1974), the natural course of which is either to remain static for many years (Williams and Hulme-Moir, 1970) or, more commonly, to progress slowly (Tanagho, 1974). This paper describes 4 patients with imperforate anus who had ureteric dilatation without vesico-ureteric reflux which resolved spontaneously.

Case Material

For 10 years it has been the routine practice at the Sheffield Children's Hospital to perform an intravenous pyelogram in the neonatal period on all patients with imperforate anus. Should this show any abnormality of the upper urinary tracts, a micturating cystourethrogram (MCU) is undertaken also.

64 consecutive cases of imperforate anus presenting in the neonatal period from 1970 to 1976 inclusive and surviving long enough to have their urinary tracts investigated were reviewed. 37 were male and 27 female. According to Stephens and Smith's (1971) classification 35 (21 male, 14 female) had high level (supralevator) lesions, 3 (1 male, 2 female) had intermediate lesions and 26 (15 male, 11 female) had low level (translevator) lesions.

2 patients had a normal IVP in the neonatal period but subsequently developed upper tract dilatation as a result of neurogenic bladder dysfunction in association with sacral deficiency.

In 4 patients the neonatal IVP revealed ureteric dilatation.

Case 1. Male, born 1970, birth weight 3.3 kg. High level lesion (anorectal agenesis with recto-urethral fistula). Associated thoracic hemivertebrae. A sigmoid colostomy was performed soon after birth. An IVP at 1 month of age (Fig. 1a) showed a solitary functioning right kidney with gross dilatation of the ureter. An MCU was normal. At 6 months of age a transabdominal pull-through operation was performed for the imperforate anus and recto-urethral fistula. At operation the right ureter was noted to be grossly dilated. The colostomy was closed 1 month later. At 1 year of age an IVP (Fig. 1b), showed almost complete resolution of the ureteric dilatation. An IVP at 6 years of age showed no deterioration. The child's control of micturition is normal but he has been constipated since closure of his colostomy. Since the neonatal period he has had multiple recurrent urinary tract infections.

Case 2. Male, born 1971, birth weight 3.0 kg. Low level lesion (incomplete covered anus). No documented urinary tract infections. A cut-back procedure was performed on the day of birth. At the age of 1 month an IVP (Fig. 2a) showed a normal left upper tract but moderate dilatation of the right ureter. An MCU was normal. At 30 months of age an IVP (Fig. 2b) showed resolution of the ureteric dilatation and a further examination at 5 years of age showed similar appearances. His control of micturition is normal. He has never been constipated.

Case 3. Male, born 1975, birth weight 3.6 kg. Low level lesion (covered anal stenosis). Associated thoracic

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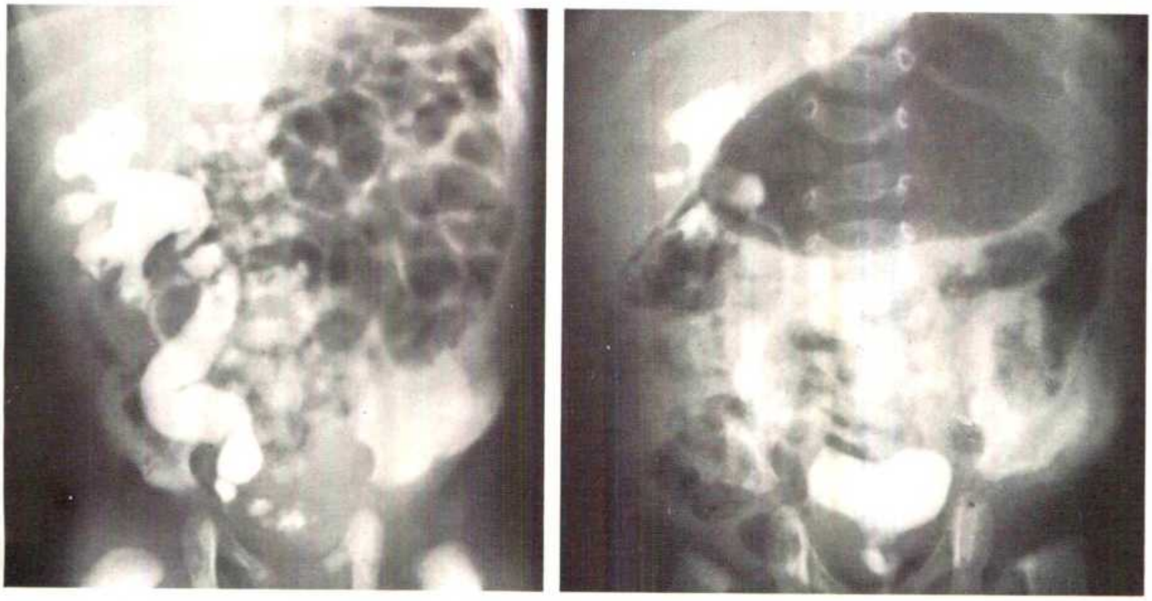

FIG. 1 Case 1. (a) IVP aged 1 month. (b) IVP aged 1 year.

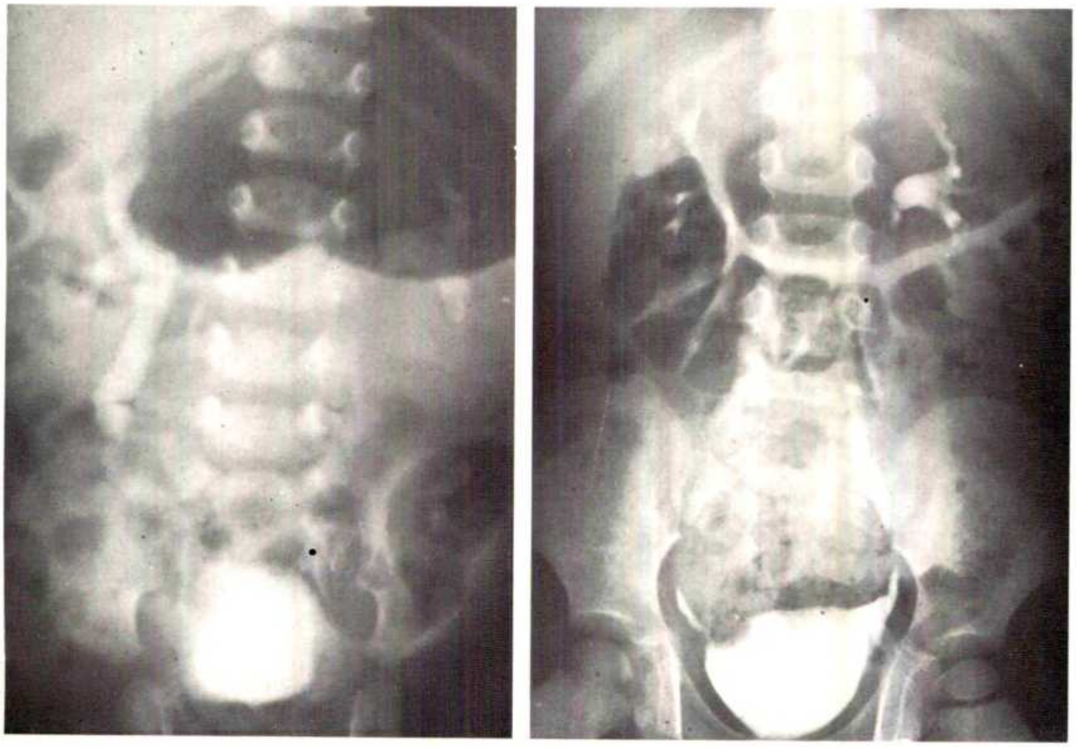

FIG. 2 Case 2. (a) IVP aged 1 month. (b) IVP aged 30 months.

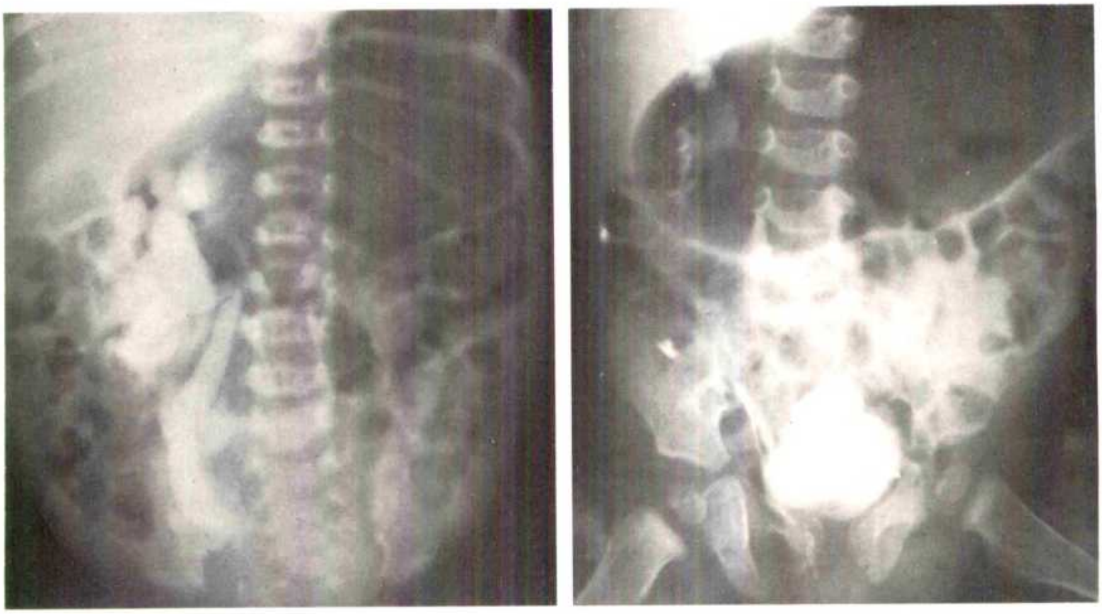

FIG. 3 Case 4. (a) IVP aged 2 weeks. (b) IVP aged 3 months. Barium from a previous examination is seen in the rectum and also in a false passage in the right side of the pelvis. The right ureter is seen just medial to this track.

hemivertebrae, talipes equinovarus and coloboma. No documented urinary tract infections. A perineal anoplasty was performed within hours of birth. His IVP at the age of 3 weeks showed a solitary functioning right kidney with ureteric dilatation of similar degree to that in Case 2. An MCU was normal. At 1 year of age a repeat IVP showed complete resolution of the ureteric dilatation. He has never been constipated.

Case 4. Male, born 1976, birth weight 3.4 kg. Low level lesion (incomplete covered anus). One documented urinary tract infection at 1 month of age. A cut-back procedure was performed on the day of birth. An IVP at 2 weeks of age (Fig. 3a) showed a solitary functioning right kidney with marked ureteric dilatation. An MCU was normal. He developed severe anal stenosis with extreme constipation and anal dilatation resulted in a false passage into the pelvis. A sigmoid colostomy was performed at 1 month of age. An IVP at 3 months of age (Fig. 3b) showed resolution of the ureteric dilatation and this appearance was maintained on a repeat examination at 1 year of age. He has subsequently had an anoplasty and closure of his colostomy.

Comment

It will have been noted that all 4 patients were male: 3 had low level lesions and 3 had solitary functioning kidneys. Since this phenomenon of transient ureteric dilatation was observed in 11% of male patients in this series it is perhaps surprising that it has not been described previously.

Although the radiological appearances were similar to those seen in primary obstructive megaureter, the spontaneous resolution of the dilatation indicates that some other explanation must be sought. Urinary tract infection would not appear to play a part. Constipation could theoretically cause ureteric obstruction, either by direct pressure on the lower ureter or by impeding the bladder outflow and causing secondary ureterovesical obstruction. Certainly constipation is a common problem in patients with imperforate anus in the early years of life. However, the degree of constipation bears no direct relation to the state of the upper urinary tracts. Several patients with low level lesions in this series were constipated from birth yet had normal upper tracts. On the other hand, constipation was never a problem in Cases 2 and 3, and a dilated ureter was found in Case 1 6 months after a colostomy had been performed. Only in Case 4 may constipation have been a factor.

Whatever the explanation of the condition, it is of more than academic interest. Firstly, if it is as common as this series suggests, then the proportion of cases of imperforate anus with *permanent* functional abnormalities of their urinary tracts may be less than that suggested by some series such as that of Singh *et al.* (1974). Secondly, and more important, since the dilatation is a self limiting condition there is no need for surgical intervention. However, it would not be surprising if, in the past, several patients did undergo operation for this quite benign condition.

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Urodynamics in Benign Prostatic Hypertrophy

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Summary—Synchronous urinary flow and pressure studies were carried out on 51 male subjects of whom 12 were normal subjects and 39 had benign prostatic hypertrophy with varying degrees of bladder outlet obstruction.

A urodynamic scoring system was evolved for accurate and objective diagnosis of bladder outlet obstruction. The minimum urethral resistance was found to be the most valuable single urodynamic parameter for the diagnosis of bladder outlet obstruction. Hitherto this urodynamic parameter was determined through tedious calculations.

In the course of the present study a new instrument, the Urethroresistance, was devised for the direct recording of urethral resistance during micturition.

6 urodynamic parameters have been found to be of value in the objective diagnosis of bladder outlet obstruction: the peak urinary flow rate (von Garrelts, 1957; Castro and Griffiths, 1972; Anikwe, 1976a); the maximum intravesical pressure (Smith, 1968; Anikwe, 1976b); the maximum detrusor pressure (Claridge, 1964; Gleason, Bottaccini and Lattimer, 1968; Anikwe, 1977a); the minimum urethral resistance (Smith, 1968; Anikwe, 1977b); the volume of residual urine (Anikwe, 1976c); and the micturition bladder wall tension (Gleason *et al.*, 1968; Anikwe, 1977c).

We were unable to find in the literature a synchronous study of all these 6 parameters either in normal subjects or in patients with bladder outlet obstruction. The present paper is a report of a urodynamic scoring system, based on these 6 urodynamic parameters, for the objective diagnosis of bladder outlet obstruction. The most valuable urodynamic parameter was identified and a new instrument devised for recording it directly during micturition.

Patients and Methods

Synchronous urinary flow and pressure recordings were carried out on 51 male subjects all of whom were over 50 years of age (53 to 82 years). The subjects were sub-divided into 5 clinical groups based on the severity of obstructive symptoms, the volume of postmicturition residual urine, the size of the prostate gland on rectal digital examination, and the degree of bladder trabeculation on cystourethroscopy. Group I consisted of 12 normal men with no clinical evidence of obstruction. 39 men had benign prostatic hypertrophy: of this group 10 patients had questionable bladder outlet obstruction (Group II), 9 had mild obstruction (Group III), and 20 had moderate or severe obstruction (Group IV). Subsequently 10 of the patients in Group IV had retropubic prostatectomy and were re-examined 6 to 10 weeks afterwards. These patients made up Group V.

The basic technique used in this study is similar to that outlined originally by von Garrelts in 1957. A 6 FG urethral catheter with side-holes near the tip was used for measuring the intravesical pressure (P). Rectal pressure (A) was measured by means of a flaccid rectal balloon. Detrusor pressure (P-A) was determined using a differential pressure transducer. All recordings were carried out with the patient standing. The zero level for pressure measurements corresponded to the upper border of the symphysis pubis. At least 4 urinary flow and pressure recordings were carried out on each subject.

Results

From each set of synchronous pressure and flow recordings for each subject peak urinary flow rate, maximum intravesical pressure, maximum detrusor pressure, minimum urethral resistance, micturition bladder-wall tension (bladder-wall tension at the commencement of micturition) and the volume of residual urine were determined. As none of the urodynamic parameters was found to maintain a

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TABLE I Minimum/maximum normal levels for non-obstructed subjects

Urodynamic Parameters	*Minimum/Maximum Normal Levels*
Mean urinary flow rate	15 ml per sec (minimum normal level)
Mean maximum intravesical pressure	102 cm H_2O (maximum normal level)
Mean maximum intrinsic bladder pressure	68 cm H_2O (maximum normal level)
Mean minimum urethral resistance	0.5 units (maximum normal level)
Mean micturition bladder wall tension	200 gm force/cm (maximum normal level)
Mean residual urine	30 ml (maximum normal level)

TABLE II Urodynamic scores for 27 subjects that have not achieved a full score of 6+ or 6−

Case	G.	F	P	D	R	T	R.U.	*Total Score*
No. 2	G. IV	+	−	−	+	−	+	0
No. 4	G. I	±	−	−	+	−	−	3−
No. 6	G. II	+	+	+	+	−	−	2+
No. 7	G. II	+	−	+	+	+	−	4+
No. 9	G. II	±	+	−	+	+	−	1+
No. 11	G. III	+	−	−	+	−	−	2−
No. 12	G. IV	±	+	−	+	+	−	1+
No. 13	G. I	−	+	+	−	+	−	0−
No. 15	G. II	±	+	−	+	−	−	1−
No. 18	G. III	+	+	+	+	−	−	2+
No. 21	G. IV	+	−	+	+	+	+	4+
No. 24	G. II	±	−	−	+	+	+	1+
No. 27	G. I	±	−	−	−	−	+	3−
No. 33	G. IV	+	+	−	+	+	+	4+
No. 37	G. II	±	+	+	+	+	−	3+
No. 38	G. III	±	+	+	+	+	−	3+
No. 40	G. II	−	−	+	−	−	+	2−
No. 41	G. III	+	−	−	+	−	+	0
No. 42	G. III	±	+	+	+	+	+	5+
No. 44	G. I	±	−	−	−	−	−	5−
No. 46	G. II	+	+	+	+	+	−	4+
No. 48	G. IV	±	+	−	−	+	+	1+
No. 49	G. IV	±	+	+	+	+	+	5+
No. 50	G. III	±	−	−	−	−	+	3−
No. 10a	G. V	±	−	−	−	−	+	3−
No. 11a	G. V	±	−	−	−	−	−	5−
No. 15a	G. V	±	−	−	−	−	−	5−

F = Mean urinary flow rate in ml per sec.
P = Mean maximum intravesical pressure in cm H_2O.
D = Mean maximum detrusor pressure in cm H_2O.
R = Mean minimum urethral resistance.
T = Mean micturition bladder wall tension in gm force per cm.
R.U. = Mean residual urine in ml.
G = Clinical group.
Case No. = Case Number.
− = Value within normal range.
+ = Value beyond normal range.
± = Urinary flow rate within the zone of overlap of 10 to 15 ml per sec.

constant level in the individual the mean of each parameter was calculated for each subject from his various recordings. Table I shows the values of various urodynamic parameters used for the separation of the obstructed from the non-obstructed subjects (Anikwe, 1976a to f). There were a number of subjects for whom all the 6 hydrodynamic parameters showed either the presence of bladder outlet obstruction or no obstruction at all. There were also other subjects for whom the diagnosis reached with the various urodynamic parameters differed. Table II shows a way of reaching an objective diagnosis for each subject using a scoring system based on the 6 urodynamic parameters. There are 6 scores each of which represents a urodynamic parameter. A value for each parameter within the limits for non-obstructed subjects is scored −ve and a value beyond normal limits is scored +ve. The scoring for mean peak urinary flow rate presents a special problem as there is a wide zone of overlap, from 10 to 15 ml per sec, between the obstructed and non-obstructed subjects. Thus while mean peak urinary flow rate of 15 ml per sec and above is scored −ve and mean peak flow rate of under 10 ml per sec is scored +ve, mean peak flow rate of 10 to 14.9 ml per sec is scored ±. 34 subjects with full scores of 6+ and 6− are diagnosed as obstructed or non-obstructed respectively. Table II represents the urodynamic scores for 27 subjects who have not achieved a full score of 6+ or 6−. The values of the urodynamic parameters of these subjects were reviewed for the presence of borderline values. Borderline values were excluded from the subsequent scores. 22 of these subjects whose revised total scores were +ve or −ve were grouped as obstructed or non-obstructed, respectively, leaving 5 problem cases (Table III). Thus apart from patients whose original total scores were zero (Case Nos. 2, 13 and 14) only 2 other patients were problem cases (Case Nos. 11 and 15).

Discussion

The urodynamics scoring system readily gives an objective diagnosis in 56 out of 61 subjects (92%). The scores for the 5 problem cases are shown in Table III.

Case No. 2 (Clinical Group IV)

In this patient with low urinary flow rate and raised urethral resistance a diagnosis of bladder outlet obstruction appears reasonable.

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TABLE III The urodynamic scores of 5 problem cases

Urodynamic Parameter	*Case No. 2*	*Case No. 11*	*Case No. 13*	*Case No. 15*	*Case No. 41*
Mean peak flow rate (ml per sec)	5.7	8.3	20.1	12.0	8.9
Mean maximum intravesical pressure (cm H_2O)	91.0	98.6	106.5	124.7	68.7
Mean maximum detrusor pressure (cm H_2O)	35.8	61.2	77.1	65.3	52.8
Mean minimum urethral resistance (in units)	1.7	1.3	0.2	0.9	0.7
Mean micturition bladder wall tension (gm force/cm)	173	191	207.7	199.4	121
Mean residual urine (ml)	117.2	5.3	6.6	27.5	87.6
Total urodynamic score	0	2−	0	1−	0

Case No. 11 (Clinical Group III)

The mean maximum intravesical pressure and the mean micturition bladder wall tension in this case have borderline values. The urinary flow rate is markedly impaired and the urethral resistance substantially raised. A diagnosis of bladder outlet obstruction is made.

Case No. 13 (Clinical Group I)

This subject has a good urinary flow and a low urethral resistance. Although the values for mean maximum intravesical pressure, mean maximum detrusor pressure and mean micturition bladder wall tension are scored +ve these values are all borderline values. In this patient the result is inconclusive.

Case No. 15 (Clinical Group II)

In this case the mean urinary flow rate is within the range of overlap of 10 to 14.9 ml per sec. The micturition bladder-wall tension and the mean maximum detrusor pressure have borderline values. Both the maximum intravesical pressure and the urethral resistance are substantially raised. It appears reasonable to make a diagnosis of bladder outlet obstruction.

Case No. 41 (Clinical Group III)

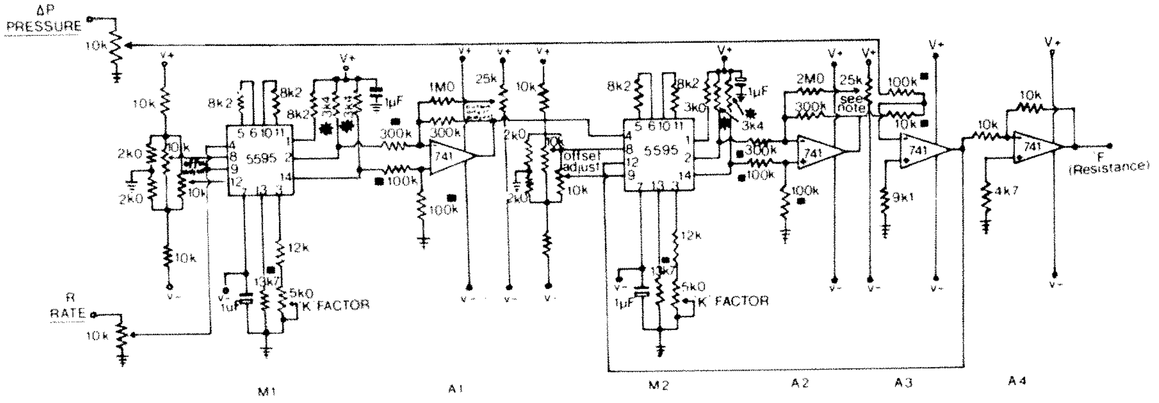
The mean urinary flow rate is considerably impaired and there is no evidence of weakness of the detrusor muscle to account for it. The urethral resistance is raised. Thus a diagnosis of bladder outlet obstruction seems justified.

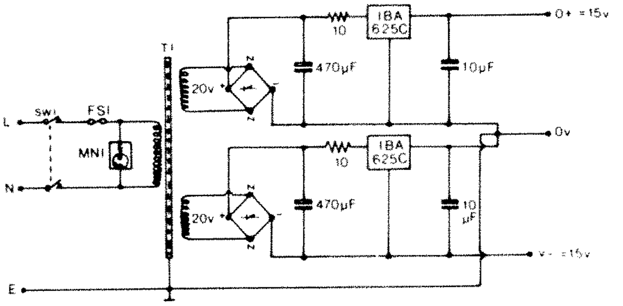
It is thus possible, using the urodynamic scoring system, to reach an objective diagnosis in 60 of the 61 cases. Furthermore, 8 out of 10 subjects (80%) with a clinically doubtful obstruction (Group II) are shown to be obstructed while the remaining 2 subjects are non-obstructed. 7 out of 9 subjects (78%) clinically diagnosed as having a slight bladder outlet obstruction (Group III) are shown urodynamically to be obstructed and the remaining 2 non-obstructed. All the 12 subjects assessed clinically as non-obstructed (Group I) and all the 10 subjects who had had a prostatectomy (Group V) are shown urodynamically to be non-obstructed. Furthermore, all the 20 patients shown clinically to have a moderate or a severe obstruction are shown urodynamically to have bladder outlet obstruction. Thus in 49 of the 61 subjects under study (80%) the correct diagnosis was reached using clinical methods solely. Urodynamic studies are thus indicated particularly for subjects who on clinical assessment are shown to have a doubtful or a slight bladder outlet obstruction.

All the 5 problem cases developed overt bladder outlet obstruction within 12 months of follow-up. Case Nos. 2 and 11 developed acute retention of urine within 6 months of follow-up and had transurethral resection of the prostate. Case Nos. 15 and 41 had a full urodynamic score of 6+ 12 months subsequently and had enucleative prostatectomy. Case No. 13 had a urodynamic score of 4+ and had transurethral resection of the prostate gland. All 5 patients benefited from prostatectomy.

From the present study determination of urethral resistance has emerged as the most valuable single urodynamic test for the assessment of the drainage of the bladder outflow tract, correct objective diagnosis having been reached in 95% of the cases. For non-obstructed subjects the mean minimum urethral resistance is found to be 0.5 units or less. All the 3 subjects for whom a correct objective diagnosis has not been reached using this urodynamic parameter were shown to have bladder outlet obstruction although the mean minimum urethral resistance was shown in each case to be within normal limits. Calculation of urethral resistance at 5 sec intervals along the urinary flow and pressure curves has shown, however, that the minimum value occurred only for a brief period usually at the start of voiding but subsequently the resistance increased rapidly. This finding underlines the importance of recording the pattern of urethral resistance (Anikwe, 1977).

Following the present study a new instrument, the "Urethroresistance", was developed for the direct recording of urethral resistance during micturition (Smith and Anikwe, 1975). The instrument is based on the formula, $P/F^2 = R$, where P is the intravesical pressure in cm H_2O, F the urinary flow rate in ml per sec, and R the urethral resistance. Figure 1 is the circuit diagram of the analogue computer for the calculation of urethral resistance. Input signal for the urinary flow rate is provided by a uroflowmeter developed by Bowley and Legg





Notes

(1) Output offset potential may require a 100 k resistor on each side if finer control is needed

(2) Resistors marked * are 0·5% ¼ watt
" " ■ " 1·0% "
" not marked " 5·0% "

(3) In the event of parasitic oscillation insert 510 Ω resistors in series with pins 4, 8, 9, 12 of the 5595.s

FIG. 1 Circuit diagram of the urethral resistance computer.

(1971) while the intravesical pressure signal is obtained via a 6 FG urethral catheter connected to a standard strain gauge transducer and amplifier apparatus. The signal for urinary flow rate is applied to both inputs of a Signetics 5595 analogue multiplier (M1) which acts as a squarer and the output converted to $-F^2/10$ by the K factor potentiometer. The differential output is inverted and made single ended by a 741 operational amplifier (A1). A second multiplier and amplifier arrangement (M2 and A2) placed in the feedback loop of a 741 amplifier (A3) forms a divider, the square of the flow rate signal being fed to the multiplier and the pressure signal coupled to the divider amplifier. The output of this amplifier is adjusted to be $-10P/F^2$. This signal is made positive by a 741 amplifier (A4) connected as an inverter. The input potentiometers on the pressure and flow rate signals are set so that an output of 1V corresponds to 0.1 cm H_2O and 0.1 ml per sec², respectively.

The "Urethroresistance" is the first device of its kind for the direct computation of urethral resistance during urinary flow. Figure 2 shows the recordings for a normal subject and for a patient with bladder outlet obstruction.

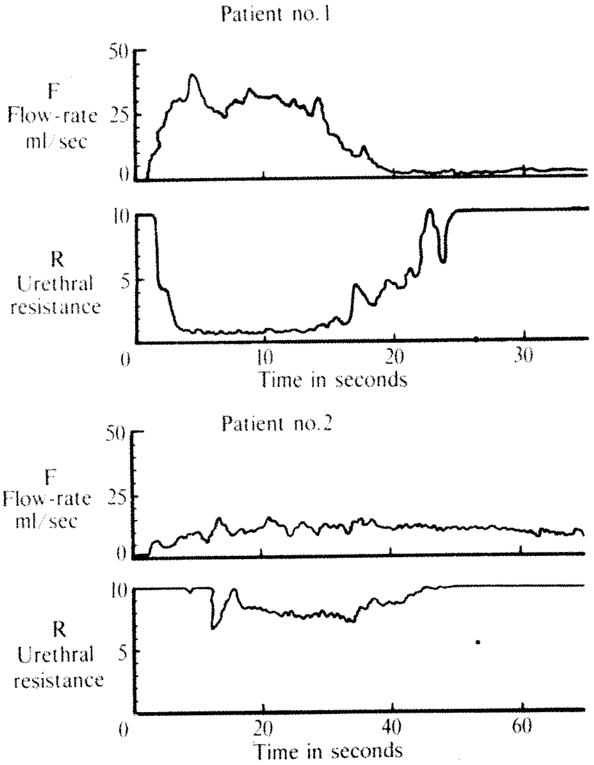


FIG. 2 Patient 1. Urinary flow and urethral resistance recordings for a non-obstructed subject. Patient 2. Urinary flow and urethral resistance recordings for a patient with bladder outlet obstruction.

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I am very grateful to Professor G. Smith, Head of Department of Surgery of the University of Aberdeen, for support and constant encouragement throughout this work. I am indebted to Mr W. H. H. Garvie and Mr J. S. Steyn of the Urological Unit of Aberdeen Royal Infirmary for constant advice and for permission to study their patients.

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Methyl Cholanthrene and Cadmium Induced Changes in Rat Prostate

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Summary—Cadmium workers have been thought to be more likely to develop prostatic cancer. The present study compares the effects of cadmium on rat prostate as compared with a known carcinogen, 20 methyl cholanthrene. The various histological effects produced are discussed.

Possibly the most important aspect is the stratification and primitive clear cells found in rat prostatic acini in cadmium injected rats.

Cadmium is a non-essential trace element which is toxic to man. It is widely used in industrial processes such as brazing, electro-plating and battery manufacture and occurs as a by-product of zinc smelting.

A suggestion that workers who used cadmium in a variety of industrial processes were liable to develop prostatic cancer prompted the present study (Potts, 1965; Kipling and Waterhouse, 1967). The effects of the known carcinogen 20 methyl cholanthrene on prostate were compared against the trace element cadmium which was given (1) direct injection into prostate and (2) subcutaneously.

Materials and Methods

The animals used were 6-week-old male Wistar rats (average weight 70 g). The animals were divided into 3 separate groups as follows:

Group I:	20 methyl cholanthrene injected directly into the ventral and dorso-lateral lobes of the prostate.
Group II:	0.05 ml of a 1 mol solution and 0.1 ml of a 1 mol solution cadmium chloride injected into the ventral and dorso-lateral lobes of the prostate.
Group III:	subcutaneous cadmium chloride injected into 5 different groups of animals in 5 incremented dosages of 0.05 ml of 1 mol solution of cadmium chloride.

The cadmium chloride was dissolved in a solution of normal saline.

Results

Group I—53 rats

As previously described 20 methyl cholanthrene produces a series of changes in rats but not in every animal (Aughey, Scott and McLaughlan, 1974). In our experiments tumours were found in 19 animals and these were predominantly sarcomas or squamous cell carcinomas (Table I). In 34 animals the deposit of methyl cholanthrene was found to be clearly present in the tissues but no obvious tumour was present. However when examined microscopically changes were present in areas of prostatic tissue surrounding the deposit of carcinogen in 26 animals.

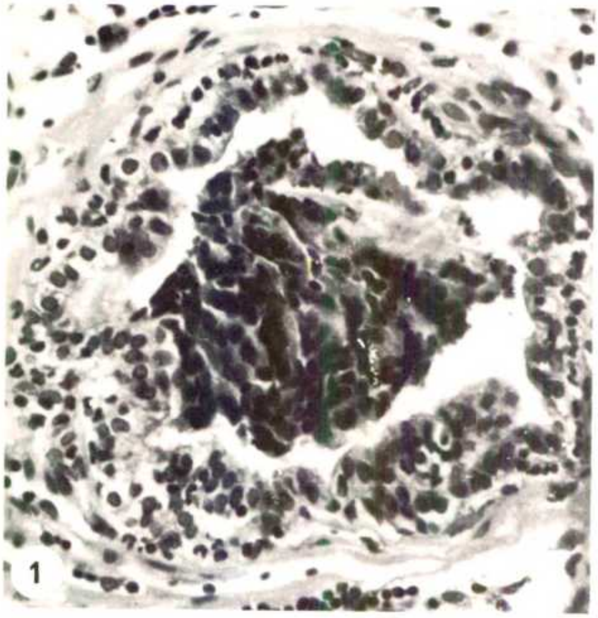
TABLE I Methyl Cholanthrene Tumours

Type	*No.*
Fibrosarcoma	11
Rhabdomyosarcoma	1
Fibrosarcoma—squamous metaplasia	2
Squamous cell carcinoma N/K	2
Squamous cell carcinoma K	3

K = Keratinising.

Methyl cholanthrene produces 3 major types of change namely hyperplasia, squamous cell metaplasia and stratification of the lining cells accompanied by the appearance of "clear" cells. The latter appear to be devoid of formed intracellular structures and are apparently very primitive cells (Fig. 1).

Read at the 33rd Annual Meeting of the British Association of Urological Surgeons in Aberdeen, June 1977.



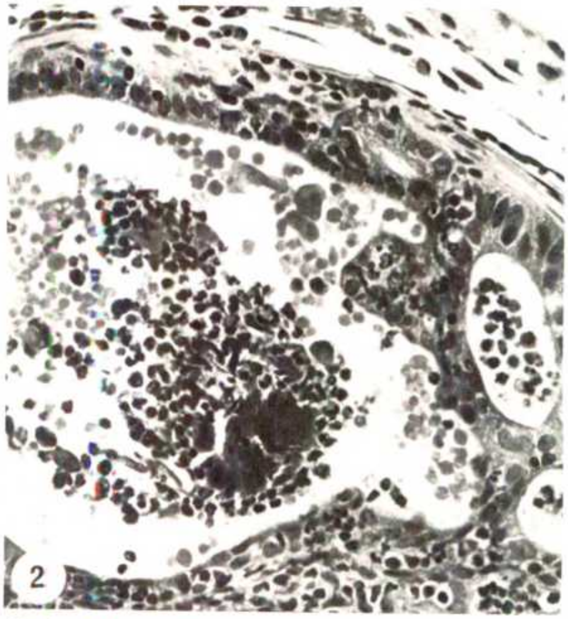


FIG. 1 20 methyl cholanthrene injection showing stratification with clear cells in the prostatic acini.

FIG. 2 Cadmium injected animal showing stratification and clear cells.

Group II—207 rats

Cadmium injected animals developed 4 distinct types of change.

1. No obvious changes—particularly in the subcutaneous injected animals.
2. Castrate regression.
3. Thickening of the basement membrane and an increase in the number of cells in the lining of the acini coupled with the appearance of clear cells (Fig. 2).
4. The development of tumours in the acini of the prostatic lobes and in the supporting structures (Table II).

TABLE II Comparison of 3 Groups

	I	*II*	*III*
Castrate regression	0	52	15
Stratification	11	80	5
Hyperplasia	7	0	0
Tumour of prostate	19	17	(1)?
Tumours—other organs	0	0	1
Normal	–	–	14

Examination of the main histological changes confirms that whereas castrate regression was not found in Group I animals it did occur in Group II and Group III animals which is consistent with the known effects of cadmium on rat testes.

The most common types of tumour found in Group II animals were tumours of the supporting tissues. (Histology was "inadequate" in all groups where animals had died over a weekend and since ultrastructural effects were a major part of this study, the carcasses were destroyed without histological examination.)

Group III—50 rats

When cadmium was injected at sites remote from the prostate, stratification and the appearance of clear cells were evident. In Group III animals a possible early adenocarcinoma has been found in an animal which had 5 injections of cadmium solution.

Discussion

Zinc is the metallic element occurring in a large number of commonly occurring enzymes, *e.g.* carboxypeptidase, alkaline phosphatase and in a group of enzymes important in protein metabolism, *e.g.* arginase, tripeptidase. There is a high concentration of zinc in liver, kidney and pancreas. Of particular interest is the high concentration of zinc found in the prostate. Commenting that the concentration of zinc was 10 times greater in the prostate than the surrounding tissues, Kar and Chowdhury (1966) noted the highest intracellular concentration was to be found in the nuclear segment of the cell. It is interesting that in carcinomatous change in the prostate the zinc content falls markedly (Schrodt, Hall and Whitmore, 1964).

Cotzias, Borg and Selleck (1961) in a study of the homeostatic mechanisms in zinc pathways in the rabbit, noted that this pathway was specific and that cadmium was the only bivalent anion which could replace zinc. They suggested that cadmium replaced zinc in the intracellular enzymes. Cotzias claimed that cadmium was an antimetabolite with respect to zinc although this is not agreed by all authorities (Webb, 1971).

It is well recognised that injection of cadmium into a rat causes acute testicular oedema with apparent recovery followed by the development of intestitial cell tumours. Gunn, Gould and Anderson (1961a) noted that these cadmium induced toxic effects on testis could be prevented by the administration of zinc. Parízek (1957) made similar observations and pointed out that the toxic effects of cadmium were only partially preventable by zinc. Not only is there an apparent competition between cadmium and zinc in rat testes but there is a complex interaction between the metals in the prostate. Even this is not simple since the dorsolateral lobe, which is under hormonal control, reacts differently from the ventral lobes (Gunn, Gould and Anderson, 1961b).

Little work has been done on the potential effects of cadmium on prostate and it is stated that cadmium, even on direct injection, has no obvious effect on the gland (Gunn, Gould and Anderson, 1967). The present experiments have clearly demonstrated that cadmium does affect the rat prostate whether by direct or indirect injection (Table III). It is hardly surprising that this should be so especially since the metal affects the testis so dramatically. When the histology of all groups is compared then it is seen that methyl cholanthrene (Group I), which exerts its effect locally on tissues, has not caused castrate regression whereas in both cadmium groups (Groups II and III) castrate regression occurs. The explanation for this is that cadmium has caused testicular damage by being absorbed into the general circulation. In Group II animals, however, there would appear to be a greater binding of cadmium at the site of injection (Aughey *et al.*, 1975) with a reduction in the testicular damage and consequently less evidence of castrate regression and a greater tendency for these animals to show stratification. What is of particular interest is that many of the changes obtained are indistinguishable from those produced by a known carcinogen (Fig. 3). As previously reported by the present authors, stratification with the appearance of primitive clear cells is a feature of cadmium induced changes in the rat (Scott, Aughey and McLaughlan, 1974).

TABLE III Comparison of 3 Groups (% changes)

Histology	*I*	*II*	*III*
Castrate regression	–	25	30
Stratification	20.75	38.6	10
Hyperplasia	13.20	–	–
C.A. prostate	35.84	8.2	2(?)
Tumours—other	–	–	2
Normal (light microscopy)	–	–	28
Histology, inadequate	32	29	28

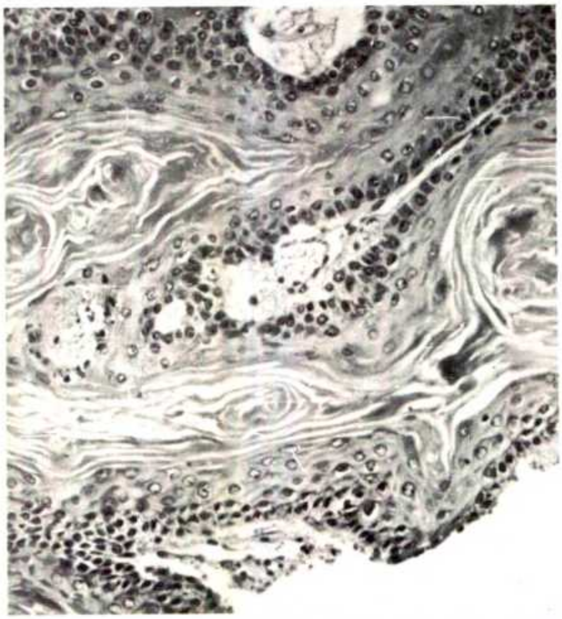


FIG. 3 Methyl cholanthrene induced squamous cell carcinoma.

It is possible that the clear cells found in cadmium injected animals could be of greater significance than has hitherto been realised. It is evident that cadmium can affect prostatic tissues and produce changes which are not unlike some of the effects produced by the metal on other tissues such as the sub-pleural connective tissue (Miller, Murthly and Sorenson, 1974).

In conclusion, the role of the non-essential element cadmium in carcinogenesis and its interaction with the essential element zinc is complicated. Zinc can obviate some of the effects of cadmium in the experimental animal and can diminish the likelihood of development of testicular tumours.

Any relation between cadmium and human cancer is not proven. There is a growing awareness that cadmium could be an important factor in genito-urinary carcinoma (Kolonel, 1975) and in view of its potential role as a zinc antagonist, merits further study.

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Prednimustine Therapy for Advanced Prostatic Cancer

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Summary—23 patients with advanced, hormonal-resistant, prostatic cancer were treated with daily oral prednimustine—a combination of prednisolone and chlorambucil. 8 patients (35%) subjectively responded with disappearance of skeletal pain and improvement in appetite, weight and sense of well being. 3 patients had objective evidence of tumour regression. Clinical toxicity was moderate, and only occasional myelosuppression was encountered.

The ease of administration and predictable toxicity of prednimustine make it a potentially useful agent, alone or in combination, for advanced prostatic cancer.

Prednimustine (Stereocyt, Leo 1031, NSC-134087)* is a combination of prednisolone and chlorambucil (Fig. 1) and has been shown effective in various malignant diseases (Möller *et al.*, 1975; Könyves *et al.*, 1975; Kaufman *et al.*, 1976). The apparent clinical effectiveness of estramustine†, an estradiol-nitrogen-mustard compound, in hormone resistant prostatic cancer (Mittelman, Shukla and Murphy, 1976) led us to try prednimustine therapy in this disease, since both, though different in constituents, may have a similar principle of action (Könyves and Liljekvist, 1976).

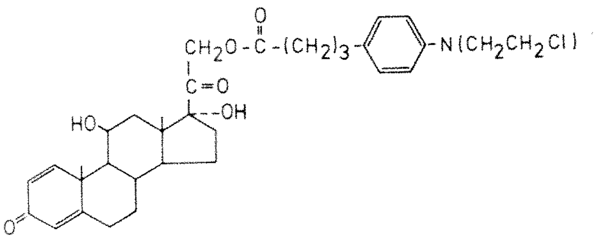

FIG. 1 Prednimustine (Leo 1031) is an ester of prednisolone (left) and chlorambucil (upper right).

Materials and Methods

23 patients who relapsed or failed to respond to adequate oestrogen therapy and/or orchidectomy for advanced metastatic prostatic cancer, were admitted to this clinical trial. The histological diagnosis and stage of disease in all patients was confirmed and clinically documented by appropriate tests in all patients who were admitted for such special study. These patients generally had, in addition to oestrogen or orchidectomy, extensive radiation therapy (>2500 rads to more than 20% of bone marrow) or non-hormonal chemotherapy (Table I). The mean age was 65 and the mean duration of disease from diagnosis to start of prednimustine therapy was 3 years. The patients were treated since April 1976 and all patients were seen and evaluated monthly. The mean duration of follow-up as of 1 June 1977 is 7 months.

Prednimustine was administered in a daily oral dose of 25 mg/M^2 and the dose was reduced to 50% if the WBC $\leqslant 3.5 \times 10^9$/l or platelets $\leqslant 0.1 \times 10^{12}$/l. The drug was discontinued if myelotoxicity (WBC $\leqslant 2.5 \times 10^9$/l and platelets $\leqslant 0.075 \times 10^{12}$/l) or other severe side effects occurred.

The responses were defined and documented according to National Prostatic Cancer Project criteria (Murphy, 1973; Scott *et al.*, 1975). Adrenocortical function was clinically evaluated in several patients by a standard ACTH test and determination of plasma cortisol level at 0, 2 and 4 hours (Sandberg *et al.*, 1957). This evaluation was selected to evaluate possible adrenal suppression by the prolonged administration of this steroidal agent. Acid phosphatase was assayed with α-naphthyl phosphate as substrate (Babson and Phillips, 1966) and the upper limit of normal in our laboratory is 4 Babson-Phillips units/ml (equal to 47 μ kat/l).

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†Estracyt, NSC-89199.

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TABLE I Response to Prednimustine Therapy

Patient No.	*Age (Yrs.)*	*Previous Therapy**	*Response †*	*Duration of Response (Months)*
1	48	E + O	Objective	13+
2	55	E + O + R + C	No	
3	51	E + O + R + C	No	
4	71	E	Subjective	13+
5	60	E	No	
6	76	E + O + R	Subjective	9
7	64	E + C	No	
8	65	E + C	No	
9	70	E + O + R	No	
10	71	E + O	No	
11	54	E + R	Subjective	5
12	78	E + O + R	No	
13	55	E + O + C	No	
14	62	E + O + R + C	No	
15	55	E + R + C	No	
16	70	E + O	Objective	3
17	62	E	No	
18	74	E + O	No	
19	67	E + O + R	No	
20	68	E + R	Objective	5
21	75	O	No	
22	59	E + O + C	Subjective	3
23	71	E + O	Subjective	3+

*E = Oestrogen Therapy
O = Orchidectomy
R = Radiation Therapy to >20% of bone marrow
C = Non-hormonal chemotherapy
NPCP Criteria (Murphy, 1973; Scott *et al.*, 1975)

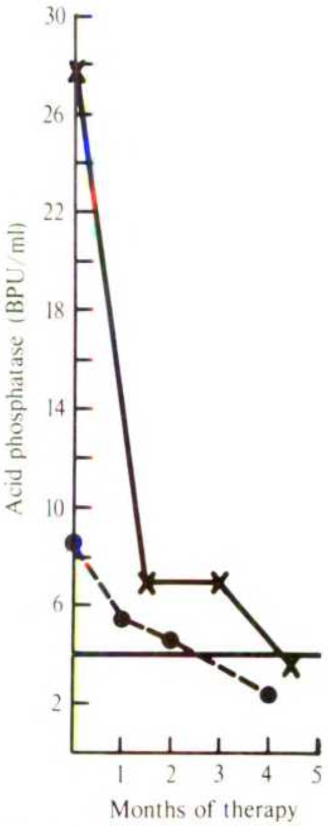

FIG. 3 Decrease of serum acid phosphatase level during prednimustine therapy (patient 16 ————, patient 20 - - - - - -). Conversion factor from BPU/ml to μ kat/l is 11.8.

Results

8 patients (35%) had a subjective response for 3 to more than 13 months (Table I). 3 patients (13%) had persistent objective signs of tumour regression. 1 of these who presented with lytic pelvic metastasis exhibited recalcification of the lesion (Fig. 2). 2 patients had a complete return of abnormally elevated acid phosphatases to normal (Fig. 3) in addition to shrinkage of an enlarged prostate.

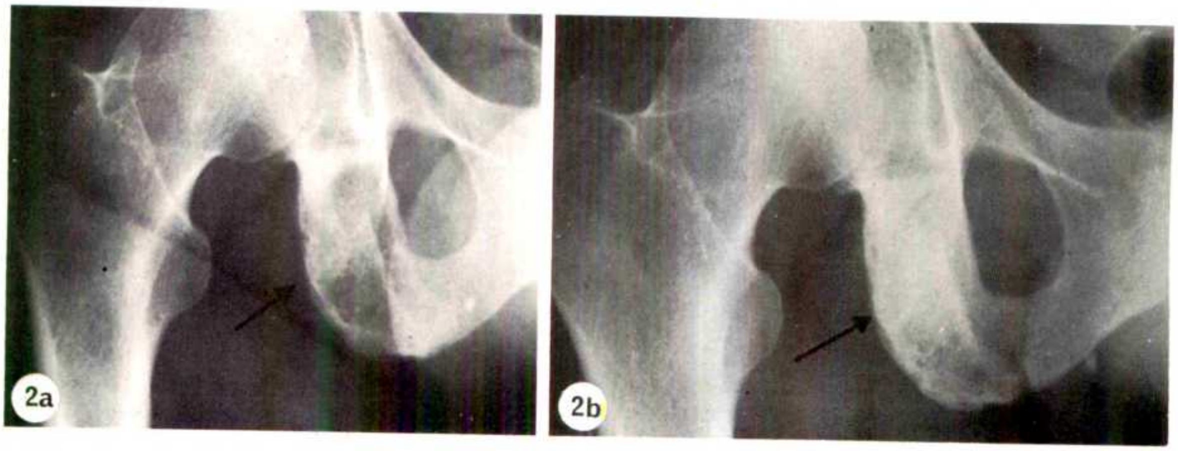

FIG. 2 Recalcification of a lytic metastasis in the right ischial area. (a) Before therapy, (b) 4 months after starting prednimustine.

TABLE II Toxic Effects of Prednimustine at a Daily Oral Dose of 25 mg/M^2

Toxicity	*Mild*	*Moderate*
Haematological	6	5
Skin rash		1
Peptic ulcer	1	

Toxicity (Table II) 11 patients developed myelosuppression, 6 were able to continue the treatment with a reduced dosage, although 5 had to stop taking the test drug. 1 developed a generalised skin rash and had to discontinue therapy and 1 had reactivation of a peptic ulcer but this subsided with antacid therapy without discontinuing the test agent. No life-threatening toxicity was encountered and all toxic side effects disappeared after cessation of therapy.

Adrenal Function ACTH tests were conducted on 4 patients at various intervals after starting prednimustine therapy (Table III). The results were within normal limits and showed that no steroid-induced adrenal suppression occurred.

TABLE III Cortisol Level (μg/dl)* in 4 Patients on Prednimustine Therapy, Before and During ACTH Infusion (7 units/hr)

Patient	*Prednimustine Treatment Duration*	*Time from start of ACTH* *0 Hour*	*2 Hours*	*4 Hours*
1	5 months	16	32	34
2	5 months	7	32	38
3	2 months	14.5	26.5	30.5
4	1 month	8	25.5	37
	Normal	(7-15)	(20-33)	(23-47)

*Conversion factor for nmol/l: 27.6

Discussion

Corticosteroid therapy has been reported to be sometimes effective in prostate cancer but this usually requires very high doses (Whitmore, 1956). Single agent chemotherapy is also effective in advanced prostatic carcinoma as shown by the National Prostatic Cancer Project but can be accompanied by severe side effects (Scott *et al.*, 1975).

Prednimustine, a synthetic corticosteroid-alkylating agent compound, has a higher therapeutic index than each of its constituents or an equimolar mixture of both (Könyves and Liljekvist, 1976). In this study, it was found to have limited but specific activity in advanced, relapsing prostatic cancer with a 35% response rate. 3 patients (13%) demonstrated objective tumour regression. The low objective response rate may partly be due to the infrequent presence of measurable soft tissue lesions in advanced prostatic cancer (Varkarakis *et al.*, 1974). The mechanism of action of prednimustine in these advanced prostatic cancer patients is not dependent on adrenal suppression, since selected ACTH tests failed to demonstrate adrenal depression during prednimustine therapy. A possible mode of action is that prostate tissue, by virtue of its steroid binding capacity, concentrates the unhydrolysed compound and later, when the alkylating moiety is discharged, the tumour is destroyed. This theory needs further confirmation although current metabolic studies of prednimustine conducted at our institute support this viewpoint (Kirdani and Sandberg, 1977).

The ease of clinical administration and lack of severe toxicity make prednimustine a useful drug in prostatic cancer. Therefore, we feel that the combination of this agent with estramustine will be feasible and will yield promising results (Catane *et al.*, 1977).

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The Measurement and Interpretation of Urethral Pressures Obtained by the Method of Brown and Wickham

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Summary—The most significant error in routine measurement of urethral pressure by the Brown-Wickham method is caused by the slow response of the system to increasing pressure. Errors due to viscous pressure losses in the measuring catheter and to variable orientation of the catheter sideholes are not normally important.

The distensibility of the urethra may be estimated from the variation of the measured pressure with infusion flow rate in the range above 2 ml/min.

In highly distensible urethras the pressure actually measured is similar to the true pressure in the undistended urethra, but in less distensible urethras this is not so.

Substantial leakage, at a flow rate of 2 ml/min or more, begins to occur when the intravesical pressure is approximately equal to the maximum pressure in the undistended urethra. Therefore, in highly distensible urethras the maximum measured pressure is a satisfactory guide to the intravesical pressure needed for substantial leakage. In less distensible urethras, however, substantial leakage may occur when the intravesical pressure is perhaps 25 cm H_2O below the maximum pressure measured in the urethra.

Leakage at very low flow rates may be possible through some urethras when the intravesical pressure is very low indeed. The urethral closure pressure profile, as ordinarily measured, is not a reliable guide to the possibility of such leakage.

With care, the method of Brown and Wickham gives satisfactory measurements of the urethral closure pressure profile. However, the maximum profile pressure exceeds, sometimes by a considerable amount, the bladder pressure needed to cause leakage.

In urodynamic investigations the pressure in the resting urethra is often measured by the method of Brown and Wickham (1969), in which a fluid is infused at a fixed, slow rate into the urethra through sideholes in a catheter. The pressure needed to drive the infusion, measured via a side-arm connection to the catheter, is taken to be the urethral pressure at the site of the sideholes. Often the measured pressure is plotted out automatically as the catheter is withdrawn through the urethra. This plot of urethral pressure against distance is called the urethral closure pressure profile. Since it is not clear that the method measures the true urethral pressure, we have made observations both on mechanical models (Martin and Griffiths, 1976) and clinically (reported here) to determine what errors and artefacts can arise. The maximum value of the urethral pressure is commonly taken as a measure of the ability of the urethra to prevent leakage. Our results show how far this is correct.

Apparatus and Material

The apparatus is in routine use at the Clinical Investigation Unit, Bristol, and is presumably typical of many similar sets of apparatus in clinical use.

The measuring catheters are of PVC, size 8 FG (Porges profile catheters, Endoscopic Instruments). 6 cm from

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the tip, and diametrically opposite each other, are 2 sideholes of diameter 1 mm. Normal saline at room temperature is infused by a Braun pump at a flow rate which can be varied in steps from 0.125 to 10 ml/min, but which in routine use is set at 2 ml/min. The signal from the pressure transducer is recorded on a moving chart (Siemens-Elema system). During profile measurement the chart is driven at 0.25 cm/s and the catheter is withdrawn steadily through the urethra at 0.7 cm/s, so that a sidehole movement of 1 cm corresponds to a displacement of 0.36 cm on the chart. Since patients are examined supine, errors due to gravitational effects are small and will not be considered.

For this work subjects were chosen as convenient from patients undergoing routine examination. All the males were over 55 years of age and had either an enlarged prostate or a urodynamic diagnosis of proximal urethral obstruction. The females suffered from stress or urge incontinence and were on average younger. The number of patients is given separately for each type of measurement. Many of these patients proved, on cystometry, to have unstable bladders. However, because all urethral closure pressure profiles were measured with the bladder empty, this caused no problem in the present investigation.

The methods, definitions and units used here conform to the standards proposed by the International Continence Society (1976), except as follows: the intravesical pressure was recorded prior to, but not during, every profile measurement; the slow rate of flow of infusion fluid through the pressure-measuring catheter is given in ml/min, not ml/s.

Possible Sources of Error in the Measurement

1. Viscous pressure losses

Because of viscosity, the pressure measured by the transducer is higher than the pressure in the catheter near the sideholes, when fluid is flowing through the catheter. We have determined this discrepancy in our apparatus by measuring the pressure needed to discharge the infusion fluid through the sideholes into the atmosphere, as a function of flow rate. The discrepancy is proportional to the flow rate, rising from essentially zero at the lowest flow rates to 6 cm H_2O (±2 cm H_2O) at 10 ml/min.

Clinically, if the infusion flow rate is not varied and if all intraurethral pressures are referred to the pressure measured when the sideholes discharge into the atmosphere at the external meatus, this potential error is automatically eliminated. However, if results at different infusion flow rates are compared, the discrepancy must be subtracted from the measured pressures. We have done this for all such comparisons in this paper.

2. Orientation of the sideholes

In dogs (Ghoneim *et al.*, to be published) and in the *fossa navicularis* of the human male urethra (Griffiths, 1971) the measured pressure apparently depends on the orientation of the catheter sideholes within the urethra, especially if there are only 1 or 2 sideholes. Clearly such an effect could lead to large errors.

We have looked for a dependence of the maximum urethral pressure on the orientation of the sideholes as follows. In each of a number of patients we recorded 6 pressure profiles, 2 profiles with the sideholes in each of 3 orientations: as first inserted into the urethra at a random orientation (0°); rotated through 90°; rotated through 180° from the 0° orientation. The infusion flow rate was 2 ml/min. Results where this flow rate was too low to produce a reliable reading of the maximum urethral pressure (see section 3 below) were discarded. This left results from 12 patients, 5 female, 7 male.

Since the 2 sideholes are diametrically opposite each other, the 0° and 180° orientations are identical. Therefore, if the pressure depends on orientation, there should be greater differences (positive or negative, at random) between the pressures measured at 0° and 90° than between those at 0° and 180°.

To test this statistically, we have calculated for each of the 12 patients the mean pressures p_o, p_{90} and p_{180} at each orientation, and the differences $p_o - p_{180}$ and $p_o - p_{90}$ between them. We have then calculated the overall variances $\sigma^2(p_o - p_{180})$ and $\sigma^2(p_o - p_{90})$ of the differences, and finally the ratio of the variances, $F = \sigma^2(p_o - p_{90})/\sigma^2(p_o - p_{180})$. If there is a significant dependence of pressure on orientation, this ratio should be significantly greater than 1. The critical value of F, given by the F-test on 11 + 11 degrees of freedom, is 2.82 ($p < 0.05$). The results are $\sigma^2(p_o - p_{180}) = 35.7$ (cm $H_2O)^2$, $\sigma^2(p_o - p_{90}) = 34.9$ (cm $H_2O)^2$, $F = 0.98$.

Therefore F is certainly not significantly greater than 1, and so there is no evidence that the maximum urethral pressure depends on the orientation of the sideholes.

3. Error due to limited speed of response

If the urethral pressure is suddenly increased, the measured pressure cannot follow it instantaneously but increases only gradually as the whole measuring system is inflated to the new pressure by the infused fluid. This rate of increase of pressure is the maximum that can be recorded by the system. Its value depends on the compliance of the system and on the infusion flow rate. It can be measured by shutting the catheter sideholes by hand and recording the subsequent pressure rise.

The effect on the recorded pressure profile depends on how fast the catheter is withdrawn through the urethra. The speed of withdrawal and the maximum recordable rate of increase of pressure with time together fix the maximum rate of increase of pressure with distance (i.e. the maximum pressure gradient) which can be measured. For instance, in our apparatus and with an infusion flow rate of 1 ml/min, the maximum rate of increase of pressure with time is 17 cm H_2O/s. The withdrawal speed is 0.7 cm/s and so the maximum measurable pressure gradient is $17/0.7 = 24$ cm H_2O/cm. At 2 ml/min the maximum rate of increase of pressure with time and the maximum measurable pressure gradient are both doubled. Figure 1 shows the effect on an actual male pressure profile. The maximum measurable pressure gradients for infusion flow rates of 1 and 2 ml/min are shown also. At 1 ml/min the profile is severely distorted and the maximum urethral pressure is not recorded. At 2 ml/min there may be slight distortion but the maximum is just registered. At 5 and 10 ml/min there is no such distortion.

When the limited speed of response causes distortion a profile of "sawtooth" shape is obtained (Fig. 1). The rising, proximal slope is equal to the maximum measurable pressure gradient, whilst the falling, distal slope is not limited in this way. Clinically this means that, should such sawtooth profiles be obtained, then the infusion flow rate must be increased or the withdrawal speed must be reduced until the sawtooth vanishes. Alternatively the compliance of the system may be reduced, *e.g.* by removing air bubbles and by using stiffer and shorter connecting lines (Brown, 1975). (In fact, with our system, careful removal of the air which normally remained in the tip of the catheter did not significantly reduce the compliance.) If this is not done the maximum urethral pressure may be greatly underestimated. Published pressure profiles which have the sawtooth shape should be regarded with suspicion.

Since the sawtooth shape appears at low infusion flow rates, it gives rise to an apparent dependence of maximum urethral pressure on infusion rate (see *e.g.* Edwards and Malvern, 1974). This dependence is however an artefact due to the limited speed of response of the system. The true dependence of the pressure on the infusion flow rate is discussed in the next section.

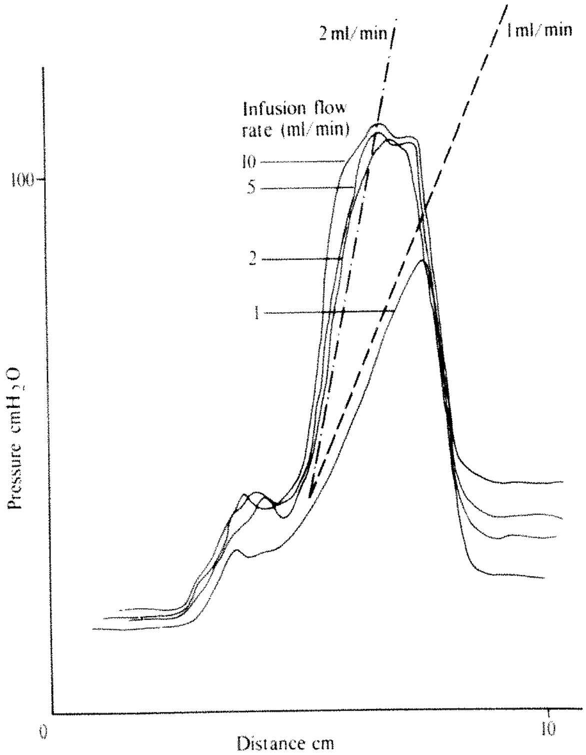

FIG. 1 Superimposed urethral closure pressure profiles from 1 male subject. The profiles were obtained by the Brown-Wickham method with infusion flow rates from 1 to 10 ml/min. The catheter, of size 8 FG, was withdrawn at a speed of 0.7 cm/s. The broken lines show the maximum measurable pressure gradients at 1 and 2 ml/min.

4. Dependence of measured pressure on infusion flow rate

If the measured pressure is truly the urethral pressure, its value cannot depend critically on the infusion rate. We have examined the dependence in 22 patients (9 female, 13 male). The catheter was held stationary, with the sideholes within 1 cm of the position of maximum urethral pressure, so that the results are not distorted by the limited speed of response of the system. The pressure measured at each infusion flow rate is plotted in Figure 2 for 3 different, representative patients. Viscous losses have been subtracted (see section 1 above). The results were obtained in order of

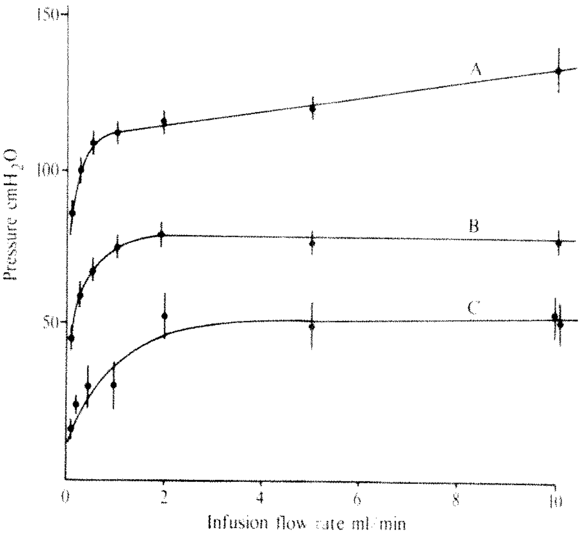

FIG. 2 True dependence of the urethral pressure, as measured near the position of maximum pressure by the Brown-Wickham method, on the infusion flow rate. Losses due to viscosity have been eliminated as described in the text. A, B: male subjects. C: female subject.

decreasing infusion flow rate from 10 ml/min to 0.125 ml/min. In some cases the flow rate was returned to 10 ml/min finally, to check the reproducibility of the results, which was satisfactory (see *e.g.* Fig. 2C).

The measured pressure depends only slightly or not at all on the infusion flow rate in the range from 2 to 10 ml/min, but falls sharply at flow rates below 1 or 2 ml/min. This behaviour is the same as that of our mechanical models of the urethra (Martin and Griffiths, 1976), in which the pressure is approximately correctly measured at the higher infusion flow rates and is underestimated at flow rates below about 1 ml/min. In the clinical measurements the difference between the pressures measured at 2 and 10 ml/min was often undetectable, *i.e.* less than 5 cm H_2O; in these cases the urethral pressure is accurately measured. In some cases, discussed in more detail in section 7 below, the difference was greater, up to 20 cm H_2O; here the urethral pressure is overestimated at the highest infusion rates.

5. Reproducibility of pressure measurements

The measurements that were used for the sidehole orientation test (section 2) may be used to investigate the reproducibility of the maximum urethral pressure. 3 pairs of urethral closure pressure profiles on 12 patients provide 36 pairs of nominally identical measurements. The standard deviation of the difference between the 2 members of each pair is 7 cm H_2O. The standard deviation for a single measurement of maximum urethral pressure is therefore similar, in fact about 5 cm H_2O. The purely instrumental contribution to this variability is estimated to be ±4 cm H_2O. Therefore the physiological variability is relatively small in these measurements, where there were certainly no obvious spasms of the urethral musculature.

Discussion: The Conditions for Leakage

6. Leakage at substantial flow rates

The accepted view is that leakage through the urethra can occur only when the intravesical pressure is equal to or slightly exceeds the maximum urethral pressure. Measurements by Cass and Hinman (1971) on the urethra of the anaesthetised female dog support this view (Griffiths, to be published). In mechanical models of the urethra, however, substantial flows can occur when the intravesical pressure is less than the maximum measured on the closure pressure profile (Martin and Griffiths, 1976). We have tested the accepted view directly in conscious male patients, by comparing the maximum urethral pressure with the pressure needed to force fluid through the urethra in a simulated leakage. So that they could be compared (see section 7 below), we made both measurements with the same, or a similar, catheter in the urethra.

The catheter, shown in Figure 3, was a modified Foley catheter. With its balloon deflated, it was first used to measure a urethral closure pressure profile by the Brown-Wickham method, and the maximum urethral pressure was noted. The balloon was then inflated in the bladder and pulled back against the bladder neck so that the urethra was sealed from the bladder. The infusion fluid, still flowing at 10 ml/min, then emerged into the proximal urethra, since the sideholes were only 1 cm from the bladder neck. Unable to escape into the bladder, the fluid inflated the proximal urethra until the pressure was high enough for fluid to leak past the peak of the pressure profile to the external meatus. This steady leakage pressure was recorded. This pressure is not the urethral wall pressure upon the sideholes, but is governed by the peak of the pressure profile.

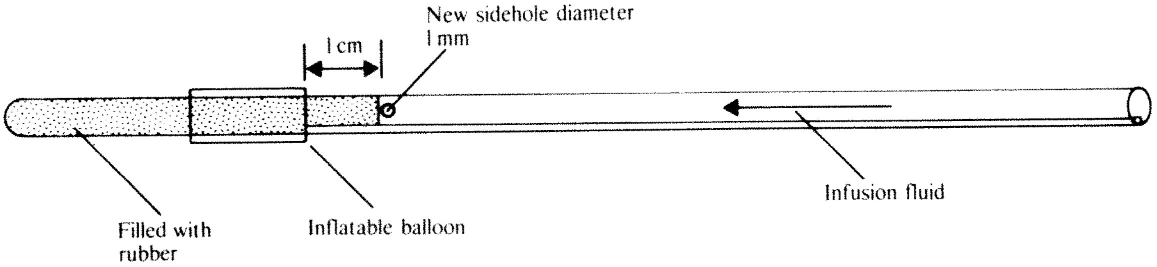

FIG. 3 Tip of a latex Foley catheter, size 8 FG, modified to measure both the urethral pressure by the Brown-Wickham method and the pressure needed to cause leakage through the urethra, as described in the text.

In 4 out of 7 subjects (males over 55 years of age) there was spasm of the urethral musculature during the measurements, as evidenced by 1 or more inconsistently high-pressure recordings of over 200 cm H_2O. For the other 3 subjects the maximum urethral pressures ranged from 68 to 130 cm H_2O, and leakage occurred at mean pressures which ranged from 13 cm H_2O below to 13 cm H_2O above the corresponding maximum urethral pressures. Therefore the accepted view, that the leakage and maximum urethral pressures should be equal, is broadly correct, although a small discrepancy cannot be ruled out.

7. *Urethral distensibility*

If one is interested in continence, the urethral pressure ought to be measured with the urethra undistended. In practice, because of the measuring catheter, the measured pressure will be greater than that in the undistended urethra, even if there are no psychological or neurogenic effects. The error involved depends on the distensibility of the urethra, *i.e.* on the extent to which the urethral pressure increases as the urethra is distended. In fact some observers have found little or no variation of urethral pressure with the size of the measuring catheter (Edwards and Malvern, 1974; Brown, 1975); others have found a significant variation (Plevnik, 1976).

We have used catheters of only 1 size, but our measurements at different infusion rates (section 4 above) allow us to estimate the urethral distensibility, near the position of maximum pressure, over a limited range of cross-sectional areas.

For infusion flow rates above 2 ml/min the urethral pressure is approximately correctly measured (see section 4 above). After viscous losses have been subtracted, the measured pressure still rises a little as the infusion flow rate is increased because the urethral wall has to be lifted further off the catheter to accommodate the increased flow: *i.e.* the urethra becomes more distended. Thus the steeper the graph of pressure against infusion flow rate (Fig. 2), the less distensible the urethra. When the graph is steep, the urethral pressure (with catheter present) is overestimated at the higher rates, by up to about 20 cm H_2O at 10 ml/min.

For a quantitative interpretation one must realise that the catheter sideholes and the local urethral wall together form an elastic constriction in the fluid path (Griffiths, 1971), from which the infused fluid escapes freely in the direction of decreasing urethral pressure towards either the bladder or the external meatus. That part of the fluid path which is downstream of the elastic constriction does not contribute to the overall resistance to flow: this is why the Brown-Wickham method is able to measure the urethral pressure near the sideholes and is not affected by the rest of the urethra. One can then calculate how the urethral pressure increases as the urethral wall is lifted off the sideholes (Griffiths, to be published), and thence estimate how it depends on the urethral diameter or circumference. In 14 of our 22 subjects (7 out of 13 males, 7 out of 9 females) the measured pressure does not depend detectably on the infusion flow rate in the range above 2 ml/min (see Figs. 2B and C). This implies that these urethras are extremely distensible: calculation suggests that the urethral pressure increases by less than 3 cm H_2O as the urethra is distended from 10 FG to 14 FG, in agreement with the observations of Edwards and Malvern (1974) and of Brown (1975). In 6 of the 13 males and 1 of the 9 females, however, the measured pressure depends quite markedly on the infusion flow rate above 2 ml/min (*e.g.* Fig. 2A). These urethras are less distensible. Calculation suggests that the pressure increases by more than 7 cm H_2O as the urethra is distended from 10 FG to 14 FG. This is an even more marked dependence than that found by Plevnik (1976). In these urethras the error incurred in assuming that the maximum urethral pressure is unaffected by the presence of the catheter may be considerable, of the order of 20 cm H_2O.

The wide variations in urethral distensibility, both between and within the male and female groups of patients, account for the disagreements among previous observers.

8. Leakage at low flow rates

Measurements at the higher infusion flow rates, although they give the urethral pressure satisfactorily, are certainly not a reliable guide to the fluid pressure needed to cause leakage from the catheter at low infusion flow rates. In our series of 22, the urethral pressures measured at 2 ml/min ranged from 115 to 50 cm H_2O, but the pressures needed to cause leakage at 0.125 ml/min ranged from 80 down to only 2 cm H_2O (cf. Fig. 2). The inference is that at very low infusion flow rates the urethral wall comes into contact with the catheter near the sideholes, without sealing them completely. Part of the urethral pressure is then supported directly by the catheter, and only part by the pressure of fluid. Certainly the behaviour at low infusion flow rates indicates the effectiveness of the seal between the urethral wall and the catheter, and in some of the urethras in our series the catheter sideholes were hardly sealed at all, even though the urethral pressure itself was reasonably high.

The seal between apposed urethral walls may be more effective than that with a catheter, but is presumably governed by the same properties of the urethral wall. Therefore our results suggest that urine may leak slowly through some urethras at intravesical pressures well below the maximum urethral pressure. It is interesting that, in our series, the female in whom the measured pressure fell consistently to the lowest values at low infusion flow rates (Fig. 2C) complained of being "constantly wet", as would be expected if there were continual, slow leakage.

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Cordopexy: A New Approach to the Undescended Testis

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Summary—Fixation of the spermatic cord, and not the testis—"cordopexy"—is a new and useful addition to an orchidopexy.

The results in 25 patients are encouraging. There has been no morbidity.

The prime object of surgery in the management of undescended testis is to provide an environment for the testis to achieve normal spermatogenesis. Over the past 150 years, at least 40 different techniques of orchidopexy, including their modifications, have been described. Each author has claimed a satisfactory result but no method is without its complications and potential adverse effects on the testis.

The technique of cordopexy as described below, is a simple one based on a new concept of fixation of the spermatic cord and not the testis; hence the name "Cordopexy". It has no adverse effect, either on the structures of the cord or on the gland, directly or indirectly and prevents slipping of the mobilised gland from the scrotum back into the groin. The testis is left hanging freely inside the scrotum.

Patients and Procedure

Over a period of 16 months, 25 patients with undescended testis were operated upon by the new technique between the ages of 4 and 21 years. Of the 25, 3 patients had bilateral undescended testes and 1 had an underdeveloped scrotum and penis.

Surgical Technique

An important step of the operation is that during mobilisation of the cord, the fascial coverings and the connective tissues of the cord are preserved as they are a vascular bed in which the testicular vessels and vas deferens are embedded. Furthermore, they are necessary for the next step of the operation which is fixation of the cord to the reflected part of inguinal ligament over the pubic tubercle. The scrotal bed is prepared by stretching the scrotum with the index finger.

A long straight needle with nylon or silk thread is passed through the stump of the gubernaculum or through the lower pole of the tunica vaginalis of the testis. Both ends of the thread are passed through the eye of a long straight needle and brought out through the fundus of the scrotum (Fig. 1). The testis is next placed inside the scrotum, care being taken to avoid twisting the cord. The assistant keeps a gentle pull on the thread so as to keep the gland inside the scrotum and to maintain the cord just taut, but with no undue tension during the fixation of the cord by stitching its fascial coverings with Dexon to the reflected part of the inguinal ligament at 1 side, and to the inguinal ligament on the other side. Either 2 such stitches on the same side, or 1 on each side of the cord at unequal levels are sufficient to anchor the cord to avoid constricting the testicular vessels but for a thick and well developed cord, 4 stitches can be used, 2 on each side (Fig. 2).

The delicate part of this step is to avoid catching the testicular vessels or vas in the stitches when the fascial coverings are picked up. After satisfactory fixation of the cord, the nylon is released to ensure that there is no retraction of the cord and that the gland remains inside the scrotum. The wound is closed in layers. The nylon is then removed from the scrotum.

Postoperative Care

No special nursing care is necessary and the patient may be allowed to go home on the seventh day after removal of stitches, or earlier with stitches in, if the home conditions are satisfactory. The patient should be advised to wear loose trousers without underpants.

Results

The early results were assessed in relation to position, size and testicular sensation, at 1 and then 6 months interval after the operation.

At operation, 15 testicles were subnormal in size and 10 were near normal in size. 7 were inside the inguinal canal; 18 were in the superficial inguinal pouch. There was no hernial sac in 6. Of the 25

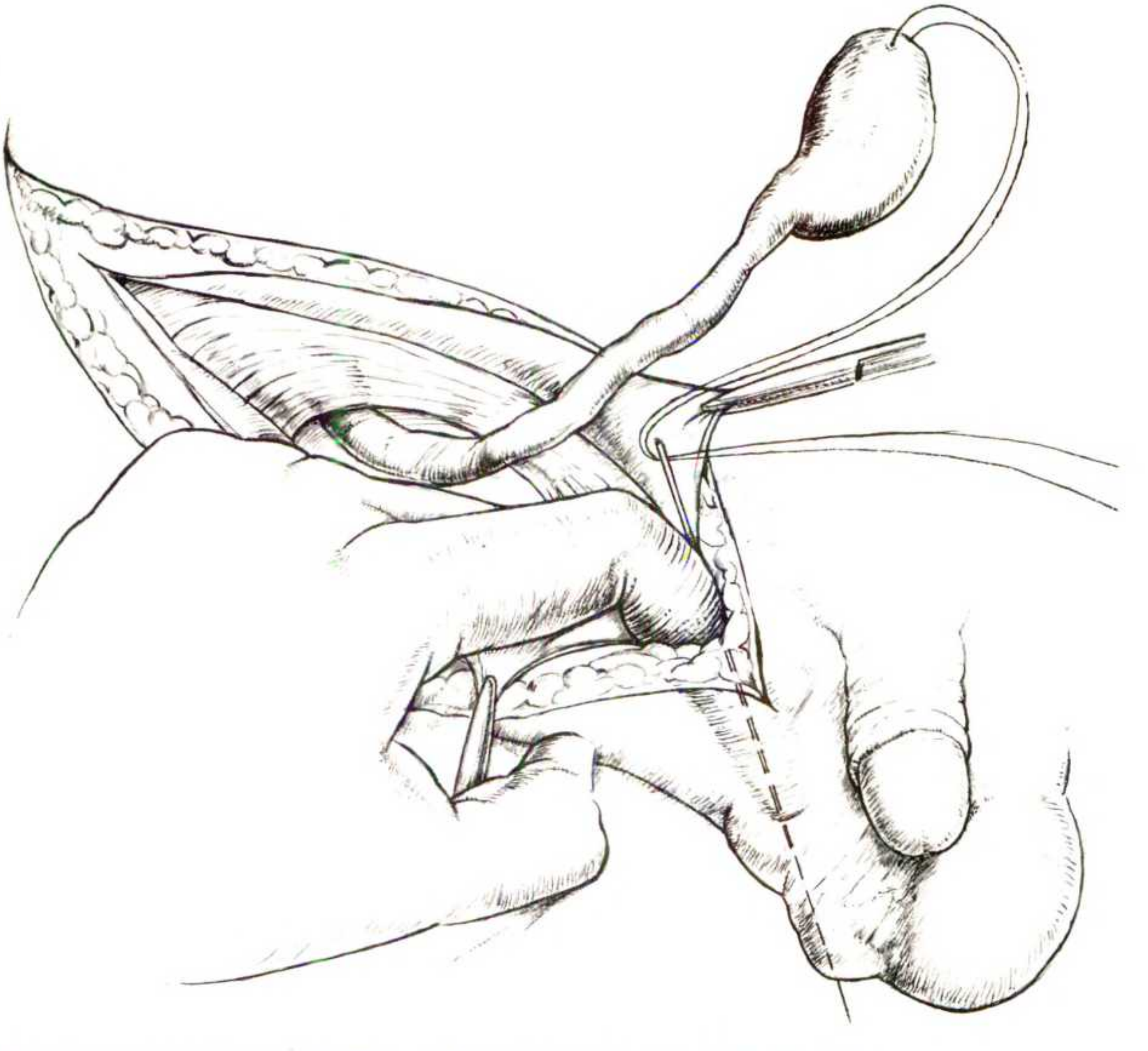

FIG. 1 Left index finger inside the scrotum for guiding the needle to pass through under direct vision.

cases, 2 were unsatisfactory when they were reviewed 6 months after operation. In 1 the testis was found inside the mid-inguinal canal and small in size; adequate mobilisation was not achieved and the testis was left high in the scrotum. After 12 months it was found further down the scrotum and appeared to be near normal in size compared to the other side.

The other patient had bilateral undescended testes with an underdeveloped scrotum and penis, and had a small testis in the superficial inguinal pouch on 1 side but, surprisingly, the poorly developed scrotum and penis became well developed and both testicles were well down inside the scrotum and noticeably larger in size when reviewed after 1 year.

There was no instance of retraction or atrophy of glands, and indeed, some testes which were small at operation were larger after 6 months.

Discussion

The principle of fixation of the testis to prevent retraction of the gland after surgery is rational, but clearly it makes sense to have something firmer than a lax scrotal wall to stitch it to.

The fascial coverings of the spermatic cord are a vascular bed in which all fine testicular vessels

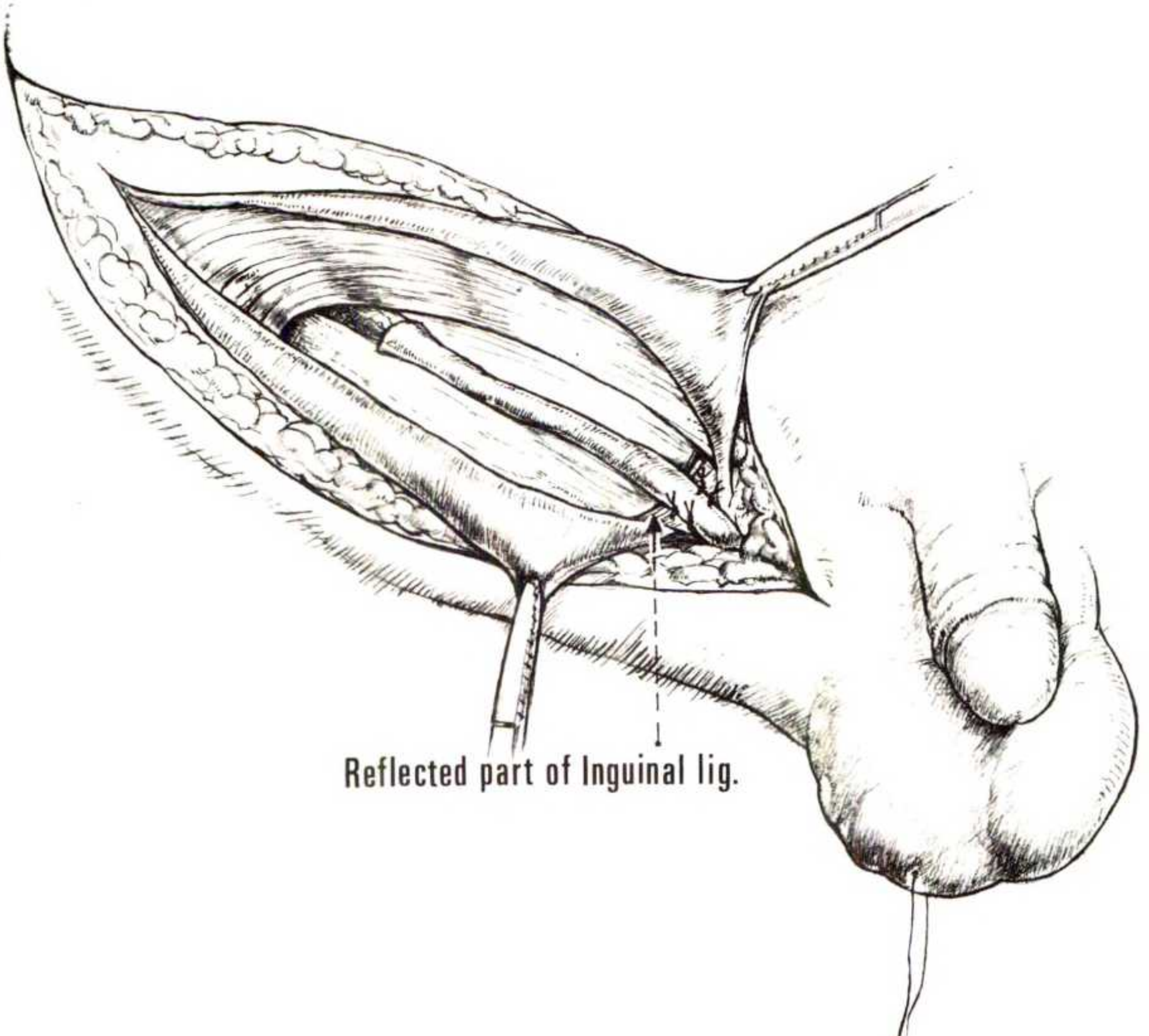

FIG. 2 Dissection of the spermatic cord at the internal ring. Fixation of the cord by 4 stitches between the fascial coverings of the cord and the reflected part of the inguinal ligament is shown. The nylon thread hanging at the bottom of the scrotum holds the testis into the scrotum and straightens the cord by a gentle pull during anchorage of the cord.

and vas deferens run together. The stripping of such fascial coverings and the connective tissues from these delicate structures as advocated by Bevan (1899) and Torek (1931) in the mobilisation of the spermatic cord is a difficult dissection which could damage the gland if the delicate testicular vessels were torn during dissection of the connective tissues.

Cordopexy is a new and simple approach. Initially, fixation of the cord to the posterior wall of the inguinal canal (transversalis fascia) was tried but this was later modified. Preservation of the fascial coverings of the distal half of the spermatic cord is an important part in this operation to allow anchorage of the cord to the area over the pubic tubercle. It has no stretching effect on the structures of the cord and prevents retraction of the gland from the scrotum after surgery. The gland is left hanging freely inside the scrotum. A healthy testis a little high in the scrotum is better than an atrophic one at the bottom (Whitaker, 1975).

Acknowledgements

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The Testes After Torsion

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Summary—In torsion of the testis a large proportion of testes saved by surgery develop secondary atrophy.

External manual reduction may be used as a first treatment, but surgical fixation is mandatory before the patient leaves the hospital.

Prophylactic fixation of the contralateral testis should always be performed as 30% of the patients will otherwise develop symptoms. The preventive operation causes no discomfort to the patient and no harm to the testis.

The fertility of the torsion patients is reduced. Patients treated for unilateral testicular torsion seem to have bilateral testicular abnormality resulting in decreased spermatogenesis.

The disaster of a testicular torsion leading to the possible loss of a gonad within a few hours is as well known as it is discouraging. Clinical examples emphasising torsion of the testis as the most important differential diagnosis in young men with acute scrotal pain and swelling, as well as the need of early exploration, have been reported with increasing frequency. Thus, the loss of 90% of 500 torted testes cited from the literature by Barker and Raper (1964) has improved into a "testicular salvage rate" of 42% (Parker and Robison, 1971), 55% (Williamson, 1976), 59% (Krarup, 1976), 63% (Chapman and Walton, 1972), or 67% (Del Villar, Ireland and Cass, 1972). However, the long-term quality of these "saved" testes and their contralateral companions remains unknown.

The author has earlier reported on 74 patients treated for torsion of the testis during a 13-year period (Krarup, 1976). This paper presents a follow-up study of 48 of these patients. It was intended to answer the following questions: (1) Do testes "saved" by detorsion really survive, or do they atrophy? (2) Is external manual reduction as safe as surgery? (3) Is prophylactic fixation of the contralateral testis necessary?—or harmful? (4) What is the fertility after torsion?

Patients

During the period 1961 to 1974 a total of 74 patients were treated for testicular torsion (Krarup, 1976). 48 volunteered for a follow-up examination in August 1974 and the findings are considered in this paper.

The mean age at torsion was 16 years and 81% were less than 20 years old. The mean observation time between torsion and follow-up was 4½ years (range 4 months to 13 years). Table I shows the method by which the patients had been treated. The patients in Groups I to V were treated in the acute stage, whereas the patients in Group VI were operated on electively because of recurrent testicular pain.

TABLE I The Method by which 48 Patients were Treated for Torsion of the Testis

Group	*Method of treatment*	*Number of patients*
I	Surgical detorsion + contralateral fixation	10
II	Surgical detorsion ÷ contralateral fixation	13
III	External manual detorsion	5
IV	Orchidectomy + contralateral fixation	9
V	Orchidectomy ÷ contralateral fixation	7
VI	Surgical fixation for recurrent pain (chronic torsion)	4

Method

The patients were interviewed by the author with reference to recurrent pain or discomfort in 1 or

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both testes, sexual function and fertility. The scrotal contents on both sides were examined by orchidometry and ultrasound Doppler technique (Pedersen, Holm and Hald, 1975) in order to estimate the size of the testes and their blood flow. 19 of the patients accepted a request for a semen analysis. Semen was analysed after not less than 3 and not more than 4 days of abstinence and within 1 hour of ejaculation.

Results

Testicular Size

In every patient the contralateral testis served as a control organ. If a formerly twisted testis was reduced in size, the difference was expressed as a percentage of the volume of the control testis. In 28 patients with "saved" testes (Table I, Groups I to III) this degree of atrophy of the formerly twisted testis is shown as a function of the time elapsed between the onset of scrotal symptoms and detorsion (Fig. 1). It is seen that only 9 testes were of normal size (atrophy "0%"), while 19 testes were more or less atrophied. The figure shows a correlation between the duration of the torsion and the subsequent diminution in size of the "saved" testis. Operation within 4 hours of torsion did not guarantee the survival of a full sized testis. The 4 patients who had testes explored electively (Table I, Group VI) had normal testes. The ultrasound Doppler investigation showed a normal blood flow in all testes, even when atrophy was marked.

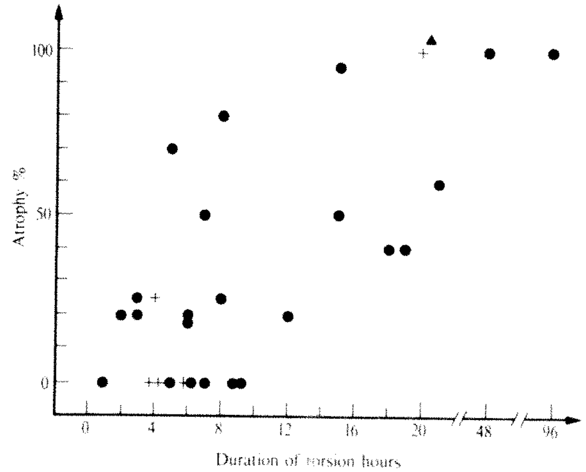

FIG. 1 The degree of atrophy of the formerly twisted testis in 28 men with "saved testes after torsion" in relation to the duration of the torsion.

- ● surgical treatment
- + reduction by manipulation
- ▲ testis lost by re-torsion.

Post-torsion Symptoms

None of the 23 patients whose testes had been reduced and fixed operatively (Table I, Groups I and II) or the 4 patients whose testes were fixed electively because of recurrent scrotal pains (Table I, Group VI) had experienced any pain, discomfort or other symptoms from the operated organ. In contrast 1 of the 5 patients who had been treated by manipulation only (Table I, Group III) had lost his testis by a misdiagnosed recurrent torsion 1 year after the first episode, and another 2 of the patients complained of intermittent swelling and pain of the testis.

The Contralateral Testis

In 19 of the patients the opposite testis had been prophylactically fixed (Table I, Groups I and IV). All of these testes were normal by palpation at follow-up and had in no case caused any symptoms. Prophylactic fixation had been omitted in 25 of the patients (Table I, Groups II, III and V). 8 of these (*i.e.* 30%) reported recurrent testicular pain, in 2 of them so often that fixation had already been performed elsewhere, and another 3 of the patients accepted admission for orchidopexy. It may be added that a further 2 patients of the original material (Krarup, 1976) had experienced torsion of their contralateral unfixed testis necessitating prompt operation. They refused follow-up.

Fertility

All patients within fertile age had a normal libido and potency. 2 married men had already been investigated because the couples were sterile. 1 patient had joined a monastery. 6 patients had produced 8 children. The remaining childless 39 patients were mostly unmarried and none of them had tested their reproductive ability.

19 of the patients delivered a sperm sample for analysis. The results of the semen analysis are shown in Table II. The semen laboratory suggested repeated analysis in half of the cases; however no attempts were made to persuade the patients to do so. Only 1 sample was characterised as within the normal fertile range. The semen quality was doubtful in 6 patients, pathological in 3, and severely pathological in 9 patients. Most of the patients had more than 1 of the parameters

TABLE II The Results of Sperm Analysis in 19 Men Treated for Testicular Torsion. The Evaluation of the Sperm Quality is Based on the Guidelines Suggested by Eliasson (1975)

Method of treatment	*Age of patient*	*Time after operation m = months y = years*	*Size of testis cm³*		*Sperms per ml (mill) (> 20)*	*Motility (good)*	*Non-viable sperms (%) (<40)*	*Abnormal heads (%) (<25)*	*Viability hours (> 48)*	***Semen quality***
			twisted	*contralat.*						
Surgical detorsion + contralat. fixation	17	8 m	8	25	131	fair	54	66	24-48	severely pathological
	22	7 m	15	20	46	fair	53	37	24-96	pathological
Surgical detorsion ÷ contralat. fixation	26	8 y	15	20	23	fair	44	78	24-48	severely pathological
	19	7 y	2	25	78	good	40	51	24-96	doubtful
	26	11 y	20	20	102	fair	34	45	<72	doubtful
	23	11 y	15	20	74	fair	25	36	>48	normal
External manual detorsion	26	9 y	25	25	56	fair	45	50	>48	doubtful
	27	6 y	0*	25	17	fair	46	52	>48	severely pathological
Orchidectomy + contralat. fixation	23	4 y		25	2.9	poor	80	78	>48	severely pathological
	27	5 m		25	39	good	43	41	24-96	doubtful
	21	3 y		25	34	good	47	50	<72	pathological
	22	3 m		25	15	poor	46	34	>48	severely pathological
	22	10 m		12	0.9	poor	80	?	<24	severely pathological
Orchidectomy ÷ contralat. fixation	24	11 y		25	12	fair	71	24	24-48	severely pathological
	26	12 y		25	35	good	37	43	>48	doubtful
	25	13 y		20	66	fair	49	71	<72	severely pathological
	20	4 y		20	9.4	good	23	32	<72	pathological
Surgical fix. for recurrent pain	16	4 m	20	20	33	good	36	27	24-96	doubtful
	29	2 y	20	5†	4.4	poor	44	62	24-96	severely pathological

* Testis lost at re-torsion.
† Misdiagnosed torsion 4 years earlier.

decreased. Even patients with a high sperm concentration had many dead or abnormal sperms. The sperm numbers seemed to be lowest among the patients who had had a testis removed. However, the differences between the different groups of patients are small and insignificant.

Discussion

The "testicular salvage rate" is a figure that states how many testes were considered suitable for being replaced in the scrotum after detorsion. It has recently been shown that 33% of saved testes atrophy within 2 years of the operation (Macnicol, 1974). In the present study the rate of secondary testicular atrophy is even greater, namely 68%, since 19 out of 28 "saved" testes were found more or less reduced in size at the follow-up.

The present study has shown a clear correlation between the duration of the torsion and the degree of subsequent atrophy. The only way to reduce the incidence of post-torsion testicular atrophy is to minimise the delay before operation. Every minute counts in this connexion. There seems to be a tendency for the manually reduced testes to remain full size more often than the operated ones. It is evident, that if external reduction is successful, the strangulation is eliminated faster than in the patient who is being prepared for operation. It must be recalled, however, that 1 of the 5 patients treated manually had lost his testis later by a recurrent torsion, and a further 2 had recurrent scrotal pain. Therefore, when torsion of the testis has been treated by external manipulation, surgical fixation is imperative before the patient leaves hospital (Sparks, 1972; Korbel, 1974).

Though most authors recommend the prophylactic fixation of the contralateral testis (Burton, 1972; Chapman and Walton, 1972; Greaney, 1975; Macnicol, 1974), Lynn (1964) argued against prophylactic fixation because of the possibility of atrophy resulting from the preventive surgery. The present study not only confirms the importance of the prophylactic fixation of the contralateral testis, it also rejects the fear of its possible subsequent atrophy. Data from the sperm counts do not offer any argument against the prophylactic fixation.

One might have expected the fertility of the torsion patients to be normal because of the presence of a normal contralateral testis. The sperm output in normal rats was not influenced by unilateral orchidectomy (Mauss and Hackstedt, 1972). However, the fertility as judged by semen analysis was normal in only 1 of the 19 men investigated. The sperm concentration varied greatly (Table II) the average of the group being 41 million sperms per ml. Nelson and Bunge (1974) examined sperm samples of 390 normal men who applied for elective vasectomy and found an average sperm concentration of 48 million per ml. Comparing with earlier accepted standards for semen analysis they concluded that over the years some unknown factor had altered the fertile male population to depress the sperm output. Nowadays the lower range of the normal sperm count is widely accepted as 20 million. A decrease of the sperm number therefore was probably the less constantly affected parameter of the semen analyses of this study. However, the viability and morphology of the sperms was markedly influenced, and these parameters seem to be more discriminatory in evaluating the fertility than the sperm density (Eliasson, 1975).

The question therefore arises whether the contralateral gonad really is normal.

Spermatogenesis in unilateral cryptorchids is often impaired. Woodhead, Pohl and Johnson (1973) found 17 out of 47 men with unilateral cryptorchidism and palpably normal solitary scrotal testes to be oligozoospermic. Lipshultz *et al.* (1976) showed that men operated on for unilaterally undescended testis at the age of 4 to 12 years had abnormal spermatogenesis when they were 21 to 35 years old, and their FSH-response to gonadotropin releasing hormone was significantly greater than in controls. The authors concluded that these results were due to bilateral testicular abnormality.

The data from the present study also suggest that patients who have been operated on for unilateral testicular torsion have bilateral testicular abnormality. Studies are now in progress to elucidate further the bilateral testicular disease in torsion patients.

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Controlled Clinical Trial of Arginine for Infertile Men with Oligozoospermia

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Summary—64 infertile men with oligozoospermia took part in a double blind cross-over trial. Each patient received matching capsules of a placebo and arginine for periods of 12 weeks. There was no difference in the conception rates of the wives or changes in the quality of the semen during each period of treatment.

Many drugs are said to improve male fertility but, unfortunately, few of them have been adequately evaluated by a controlled trial. Arginine is an amino acid which was shown by Holt and Albanese in 1944 to be necessary for human spermatogenesis. They fed 3 volunteers on an arginine deficient diet and after 9 days there was such a dramatic fall in sperm density and motility that the experiment was discontinued. They then treated 5 men with oligozoospermia and found that in 2 patients there was an improvement in the sperm density and motility.

Arginine has been used intermittently since that time with conflicting reports being given of its efficacy. The most favourable report was that of Schachter, Goldman and Zukerman (1973) who found that 74.6% of 178 oligozoospermic men were improved by arginine. In order to assess the efficacy of arginine a double blind clinical trial was designed to see whether arginine would improve the fertility of an infertile couple where the man had severe oligozoospermia.

Method

64 male partners of an infertile marriage, attending King's College Hospital, London, or St Peter's Hospital, were admitted to the trial, having fulfilled the following entry criteria:

1. Total motile sperm count of less than 10 million per ejaculate on each of 2 occasions immediately preceding the trial.
2. No uncorrected varicocele or testicular maldescent.
3. Testicular biopsy already performed (Johnsen, 1970).
4. No drugs taken in past 3 months which were known to affect spermatogenesis.
5. No history of biliary disease owing to a suggestion that arginine might interfere with the metabolism of bile salts.

The wives of all these men had been fully investigated with regard to fertility. During the trial each man had a seminal fluid analysis performed monthly by the same technician—the specimen being produced by masturbation after 3 days of continence. Sperm motility was assessed at 3 hours to obtain uniformity for specimens produced at different hospitals. Plasma follicle stimulating hormone (FSH), luteinising hormone (LH) and prolactin were estimated at the start of treatment and at 12 weekly intervals. Albuminuria was also sought at these times but with negative findings throughout.

The trial was conducted as a double blind cross-over trial comparing arginine 4 g daily with matching placebo capsules. Each treatment period lasted 12 weeks with no intervening wash-out period. The first treatment was allocated at random and 35 of the 64 patients received arginine first.

Results

8 patients failed to complete the 24 weeks of treatment (1 of them discontinued treatment when his wife conceived) and 2 patients were azoospermic throughout. These 10 patients are excluded from the analysis. 9 patients were found to have more than 10 million sperms in 1 of the pretreatment seminal analyses but these patients have not been excluded.

Read at the 33rd Annual Meeting of the British Association of Urological Surgeons in Aberdeen, June 1977.

TABLE I Details of the 6 Men whose Wives Conceived

Patient	Initial density (10^6/ml)	Semen motility (%)	Biopsy*	FSH (u/l)	Treatment at conception	Total motile sperm count Initial	Total motile sperm count At conception
1	1.5	21	8.4	9.3	Placebo† ‡	1	1
2	1.5	25	9.4	2.6	Placebo†	1	1.4
3	1	30	6.6/6.5	0.3	Arginine†	1	17
4	3	60	8.1/8.4	2.0	Arginine†	2.9	19.7
5	2.3	58	6.5/2.0	4.1	Arginine	4.8	1.3
6	4.5	33	8.6	2.5	Following Treatment	3.2	47

* Mean Johnsen score.
† Conceived during first month of treatment.
‡ Failed to attend once wife conceived.

Conception Rates

The wives of 6 men became pregnant as is shown in Table I. This shows that pregnancies occurred regularly even with poor quality semen, impaired spermatogenesis, or elevation of the FSH. Conception occurred on 4 occasions within 1 month of starting the trial (twice each with placebo and arginine) and 1 conception occurred the month after completing the trial. There was no difference in the conception rates during the 2 periods of study.

Semen Quality

Changes in semen volume, sperm density, motility and percentage of abnormal forms showed no difference which could be related to the treatment. Figure 1 shows that the percentage of patients showing an increase in sperm density or motility was the same in both groups as was the percentage of patients reaching a target sperm density.

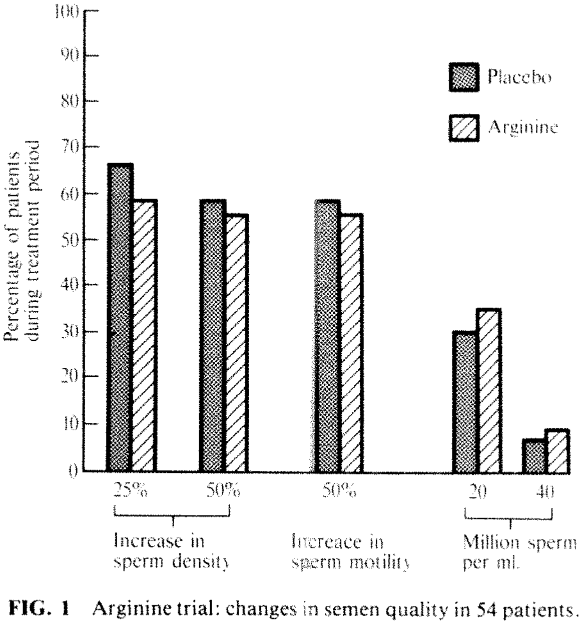

FIG. 1 Arginine trial: changes in semen quality in 54 patients.

In an attempt to show whether there were any factors which correlated with the prognosis those patients who showed an improvement at the end of a treatment period were compared to the remaining patients. An improvement was judged to have occurred in the 13 whose total motile sperm count was more than 100% greater than the better of their 2 pretreatment values.

TABLE II Relationship between Conception, Improvement in Semen and Initial Total Number of Motile Sperms

Total motile sperms (millions)	Conception	Improved	Not improved
<1	2*	3	20
1-5	4	8	10
6-10		0	4
7-10		2	7

* Includes patient who withdrew when wife conceived.

The initial semen quality was not related to subsequent improvement (Table II) but patients with impaired spermatogenesis on the testicular biopsy, or elevated on FSH, were less likely to show any improvement during treatment (Table III). The luteinising hormone was normal in nearly all the patients and the prolactin levels were variable but without any definite pattern. A more surprising and significant finding was that all the pregnancies and 12 of the 13 patients with improved semen came from 1 end of the trial (Table III).

The semen quality and testicular histology showed a similar range but the admission of

TABLE III Relationship between Testicular Histology, FSH, Treatment Centre, and Conception or Improvement in Semen Quality

	Conception	*Improved*	*Not improved*
Reasonable Spermatogenesis	4*	10	9
Impaired Spermatogenesis †	2	2	13
Normal FSH	4	11	17
Elevated FSH	2	2	21
Centre A	6	12	24
Centre B	0	1	17

* Includes patient who withdrew when wife conceived.

† Impaired spermatogenesis when Johnsen score less than 8.0.

patients reflected different outlooks. 1 physician spoke positively of the chance of improvement whereas the other entered patients only if all other treatment options had failed.

Discussion

The assessment of fertility is difficult and the conception rate must be the ultimate yardstick to assess the efficiency of any treatment. In the present trial we observed a conception rate of about 10% of wives in the first 6 months of the trial and the conception occurred with equal frequency during the period the husband was taking the placebo or arginine. This conception rate is similar to that found in most reports of drug efficiency in male fertility (about 20% per annum).

The relationship between fertility and the quality of the semen is less certain but Macleod and Gold (1951) and van Zyl *et al.* (1975) both found that the chances of conception were slightly reduced with a sperm density of 10 to 20 million per ml, but below this level there was a much greater fall in the conception rate.

The variability in the semen quality makes it essential to use a standard technique for the collection and examination of the semen and to repeat the tests in a pretreatment period. 3 examinations over a 3-month period would give a better indication of the normal range than the 2 used in this study. In assessing the results of treatment it is necessary to define what constitutes an improvement and changes in any quality of the semen during treatment have to be compared to the best value in the pretreatment range. There is some justification for looking at changes in the total motile sperm count as this value remains fairly constant, as an improvement in sperm density is often accompanied by a fall in sperm motility. It is also important to observe the individual variables as a patient with a persistent low motility has a different problem from one with a reduced number of sperms with normal motility.

The meaning of a percentage improvement in any quality of the semen varies with the original level. A 50% improvement in the number of spermatozoa in a man with 5 million sperms per ml is of more importance with regard to fertility than a 50% improvement in a man with 30 million spermatozoa per ml. It is also useful to compare the number of patients who achieved a set target of spermatozoa as when there are more than 20 million spermatozoa per ml there is little change in the conception rate with increasing sperm density (Macleod and Gold, 1951; and van Zyl *et al.*, 1975). In this study both methods were used and neither method of assessment showed any advantage for arginine as compared with the placebo. This may be due to the adequacy of arginine in the diet of our subjects.

In assessing the results of any trial the importance of allocating the treatment and the placebo on a double blind basis is clearly shown. That an improvement should occur during the period of placebo therapy is sufficient ethical justification for the use of placebo control. The discrepancy in the improvement occurring in the 2 centres is difficult to explain but the role of the psyche in fertility is well established. At the present time, however, it is not possible to say that this accounts for the difference for although the initial semen, hormone studies and testicular biopsies of the centres were comparable it is possible that at 1 centre the patients had previously failed to respond to more methods of treatment.

Conclusion

Arginine was no more effective than the placebo in improving fertility or the semen quality of infertile men with severe oligozoospermia.

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We should like to thank Mrs Helena Shaw for her expert supervision of the trial, and E. Merck Ltd for supplying the capsules of arginine and placebo.

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British Journal of Urology (1978), **50**, 51

Case Reports

Bilateral Pelvic Ectopic Kidneys

Unilateral pelvic ectopic kidney is not an uncommon finding and this congenital anomaly may be encountered during routine urological investigation.

Bilateral pelvic ectopic kidneys seem to be very rare. The anomaly is mentioned in textbooks but we have not found any case report; there is an X-ray picture in Emmett's textbook *Clinical Urography*.

Recently we have seen 2 cases of bilateral pelvic ectopia.

Case Reports

Case 1. A 65-year-old male was admitted for prostatectomy and on routine IVP before operation bilateral pelvic kidneys were found (Fig. 1).

Case 2. A premature baby was admitted at age 2 months for investigation because of urinary tract infection, and on routine IVP bilateral ectopic kidneys were found (Fig. 2).

Comment

Ectopic kidney is clinically important. The involved organ is abnormally liable to infection and stone formation. It may cause pressure on neighbouring organs and produce abdominal symptoms. Palpation of the kidney may lead to incorrect diagnosis of neoplasms or other disease of another organ. Technically, surgical treatment may be extremely difficult.

In bilateral ectopic kidneys all of these symptoms may be exaggerated and conservative treatment should be adopted.

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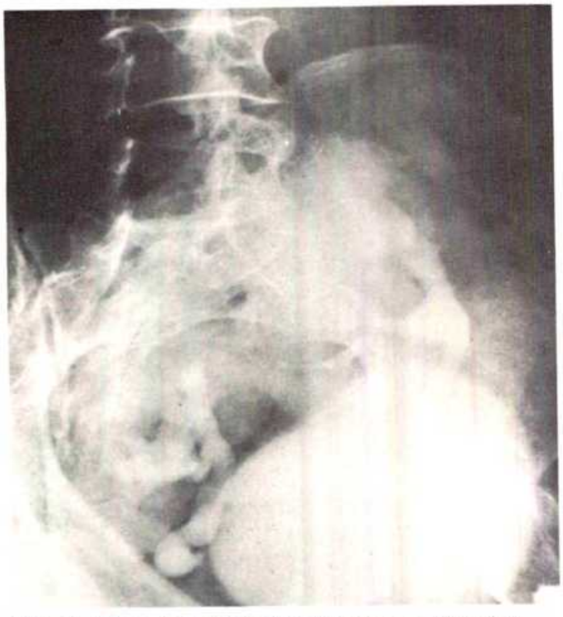

FIG. 1 Bilateral ectopic kidney in a 65-year-old patient.

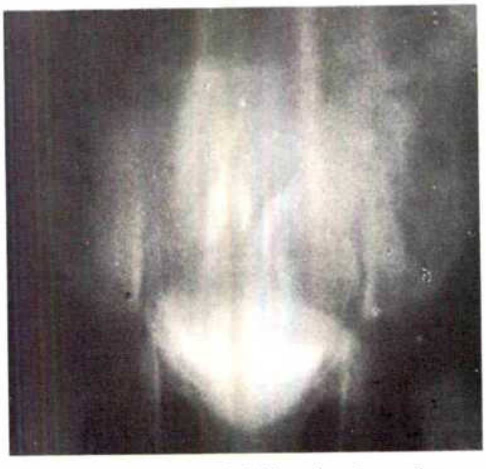

FIG. 2 Bilateral ectopic kidney in a 2-month premature baby.

British Journal of Urology (1978), **50**, 52

Single Case Report

Intimal Tear, Cause of Transplant Failure

Mechanical injuries during preservation have been postulated as a cause of kidney transplant failure but this has never been reported. A typical example of this type of problem is presented.

Case Report

A 22-year-old woman with end-stage kidney disease due to chronic glomerulonephritis received a transplant from a cadaver donor. The donor's renal artery had an aortic cuff and was anastomosed to the external iliac artery. The patient remained anuric after the operation. A renogram and angiography performed the day following transplantation indicated no vascularisation of the transplanted kidney. At surgical exploration the transplanted kidney was dark pink coloured, flabby without tonus. There was no pulsation of the renal artery and on compression of the renal vein there was no swelling of the kidney. Nephrectomy of the transplant was performed.

The histological examination of the main renal artery showed complete disappearance of the intimal lining, injury of the internal elastic lamina and obstruction of the lumen of the artery by a recent thrombus (Fig. 1).

Comment

Renal artery thrombosis following transplantation in the early postoperative period has been attributed to acute humoral rejection, a hypercoagulable state, or a tear in the intimal suture line of the recipient hypogastric artery (White *et al.*, 1972). Intimal damage, especially during cannulation for irrigation or perfusion, was discussed but never demonstrated in the past (Smellie, Vinik and Hume, 1969). The injury caused by this mechanism did not result in the immediate loss of the transplant and the occurrence of renal artery stenosis was more blamed on this mechanism than was renal artery thrombosis (Beachley *et al.*, 1976).

In the case presented the renal artery thrombosis in the early postoperative period was related to excessive intimal injury. The catheter, forcefully introduced into the renal artery during the preservation caused stripping of the intima with injury of the internal elastic lamina and thrombosis of the artery. Thus technical failure of the transplant with immediate loss of it may be caused during the extracorporeal preservation manipulation.

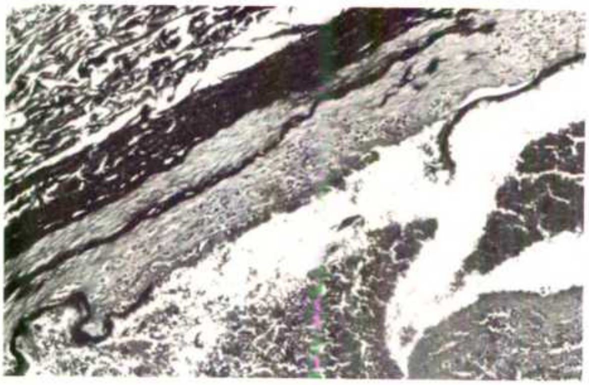

FIG. 1

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British Journal of Urology (1978), **50**, 53

Single Case Report

An Unusual Case of Cavernositis

A 38-year-old West Indian presented with a 6-month history of painful erections. His penis deviated to the left on erection and intercourse became impossible. The onset was gradual and there was no history suggestive of an attack of priapism. The physical signs were remarkable. Both corpora cavernosa were hard and uniformly indurated the whole length of the penile shaft while in the perineum the crura were similarly affected. X-ray showed the lesion to be calcified (Fig. 1). An attempt was made to perform a cavernosogram but dye could not be injected into the corpora as the fibrous tissue was so dense. As the physical signs were unusual biopsy was performed and histology showed a mass of fibrous tissue compatible with Peyronie's disease (Fig. 2). After 6 months' treatment with potassium aminobenzoate he reported improvement in that his penis was softer and intercourse less painful, but objectively the physical signs were unchanged.

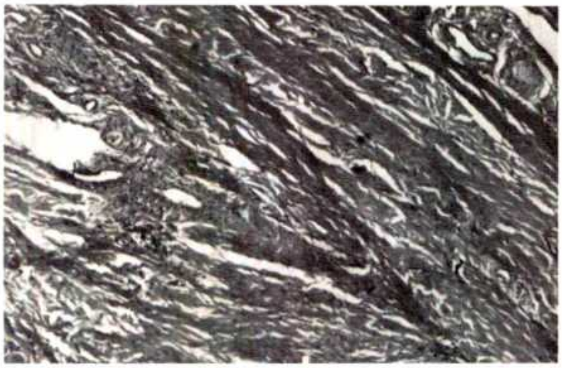

FIG. 2 Photomicrograph of biopsy taken from the left corpus cavernosum showing extensive fibrosis. (H & E. x 25.)

Comment

No description of a similar case has been found in the literature. Characteristic of Peyronie's disease are single or multiple circumscribed plaques which involve part of 1 corpus cavernosum or part of both corpora (Blandy, 1976). Lowsley and Boyce (1950) refer to cases where a plaque extended the length of the penis and Winsbury-White (1948) refers to infiltration of the whole body of the corpus but in neither instance is there detailed description. Other rare causes of penile induration are syphilis and lymphogranuloma venereum and these were excluded by the appropriate serological tests. The precise cause of the cavernositis in this case therefore remains obscure.

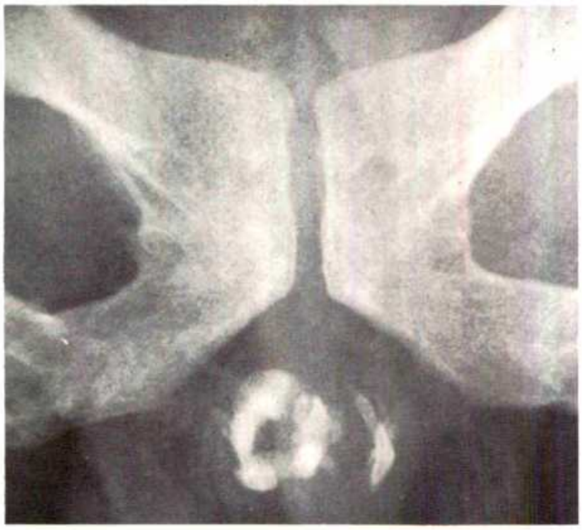

FIG. 1 X-ray showing penile calcification.

Acknowledgements

I wish to thank Dr G. Jelinek and Sir Harry Annamunthodo for their advice and permission to publish this report. I also thank Dr L. W. L. Horton of the Department of Pathology.

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British Journal of Urology (1978), **50**, 54

Single Case Report

Severe Hypertension following Traumatic Renal Infarction

A 19-year-old male was admitted to hospital following a road traffic accident. He had sustained paraplegia (sensory level D11) with multiple fractures of the lumbar transverse processes and lower ribs. Haematuria was noted. An IVP showed a normal right kidney and a non-functioning left kidney.

At laparotomy, 8 hours after injury, bilateral retroperitoneal haematomata were found but renal exploration was not performed. 7 days later he was transferred to a spinal injuries unit. The blood pressure at that time was 140/80.

11 weeks after injury, headache, neck stiffness and vomiting developed associated with a blood pressure of 240/150. Renal arteriography (Fig. 1). showed complete obstruction of the 2 left renal arteries.

The left kidney was explored. It was surrounded by dense, fibrous tissue. No renal artery pulsation was detected. Nephrectomy was performed.

Histological examination of the excised kidney showed almost complete infarction.

2 days later the blood pressure had fallen to 120/80. The blood urea and serum creatinine levels were normal. These findings were unchanged at a recent follow-up examination 12 months after operation.

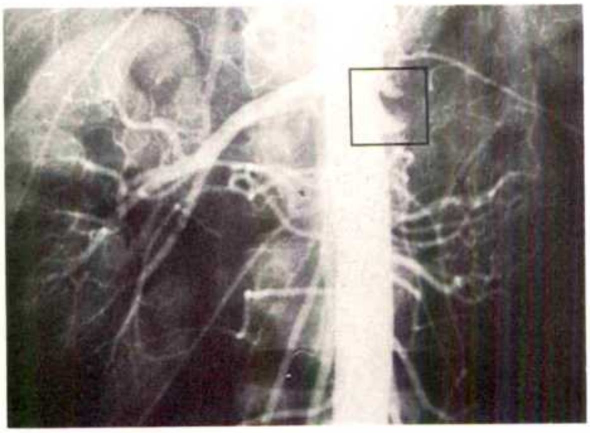

FIG. 1 Renal arteriogram showing obstruction of the 2 left renal arteries.

Comment

This case is unique to the British literature and provides an extreme clinical counterpart to Goldblatt's animal experiments (Goldblatt *et al.*, 1933).

The mechanism of renal artery injury was reviewed by Mogg and Evans (1971). Sudden deceleration is presumed to cause acute arterial angulation with intimal laceration. Later an obstructing thrombosis occurs.

Renovascular hypertension may occur when no renal perfusion is demonstrated at arteriography. The onset of the symptoms of hypertension may occur many weeks after the initial injury.

The need for careful follow-up of cases of renal trauma is stressed to avoid the potentially disastrous complication of severe hypertension.

Acknowledgements

We would like to thank Mr L. S. Scott and Mr A. G. Hutchison for their help.

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British Journal of Urology (1978), **50**, 55

Points of Technique

An Instrument for Intrarenal Irrigation

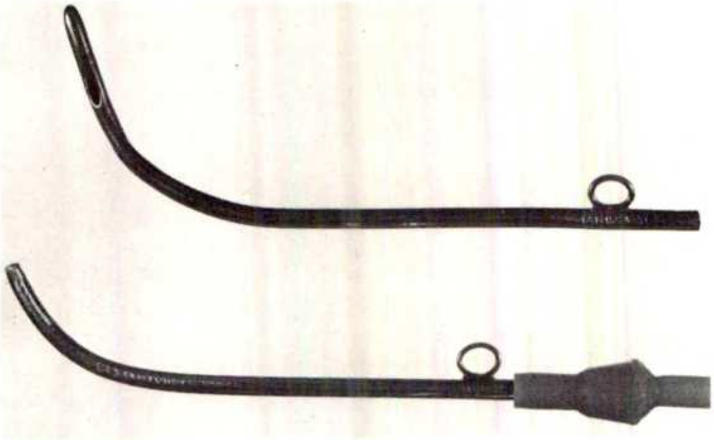

FIG. 1

Irrigation of the pelvic-calyceal system is easier and more effective using an instrument made from a female metal urethral catheter. This instrument has already been described as an aid in intra-operative ureteric catheterisation (Pearson, 1970).

The catheter is cut across above the lateral opening, curved and the end smoothed. It is attached to an intravenous giving set (Fig. 1). Fluid can then be run in under pressure as required. The advantages are: it is easily attached to a giving set; continuous irrigation with as many litres as required; it can be used to irrigate other sites; is easily held in the required position (Fig. 2), its position inside the kidney is certain—without bending or kinking; and calculus debris is washed out from the innermost calyces.

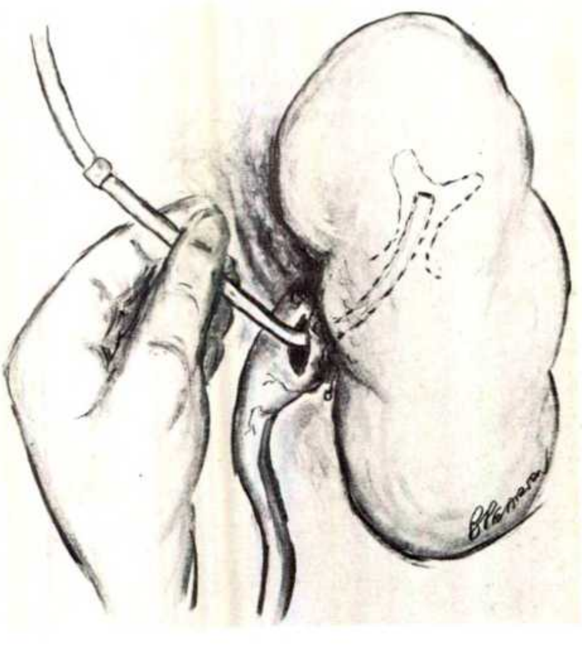

FIG. 2

Reference

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British Journal of Urology (1978), **50**, 56

Points of Technique

Method of Mobilising the Adherent Obstructed Ureter

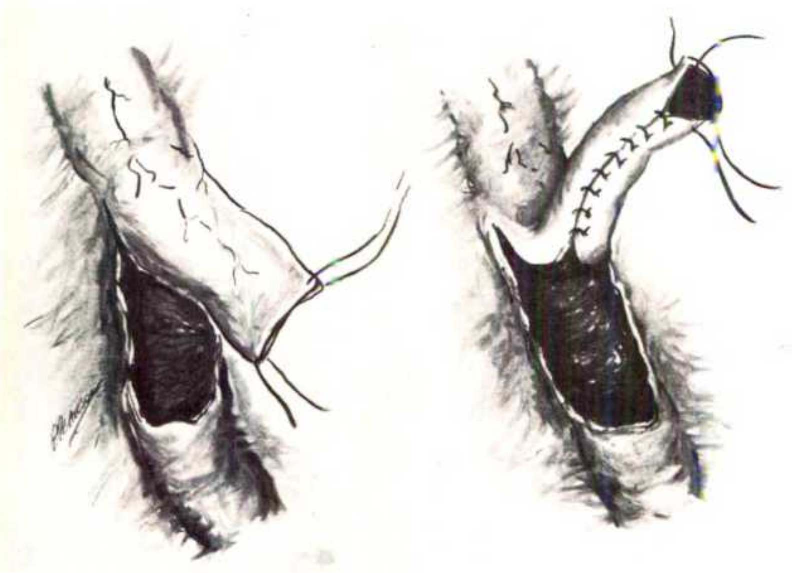

FIG. 1

A grossly obstructed ureter may be so adherent to the posterior abdominal wall or iliac vessels that it cannot be mobilised. When the ureter is sufficiently dilated, a tube may be fashioned from the anterior wall of the ureter (Fig. 1) and the tube thus formed may then be anastomosed, for example, to a Boari flap (Fig. 2). It is recommended that a splint is used across the reconstructed ureter and anastomosis.

Leaving the posterior wall of the ureter *in situ* avoids damage to the ureter by excessive dissection. Structures to which the ureter is adherent are not damaged.

This method has been used successfully in 2 cases of severe obstruction following post-irradiation fibrosis.

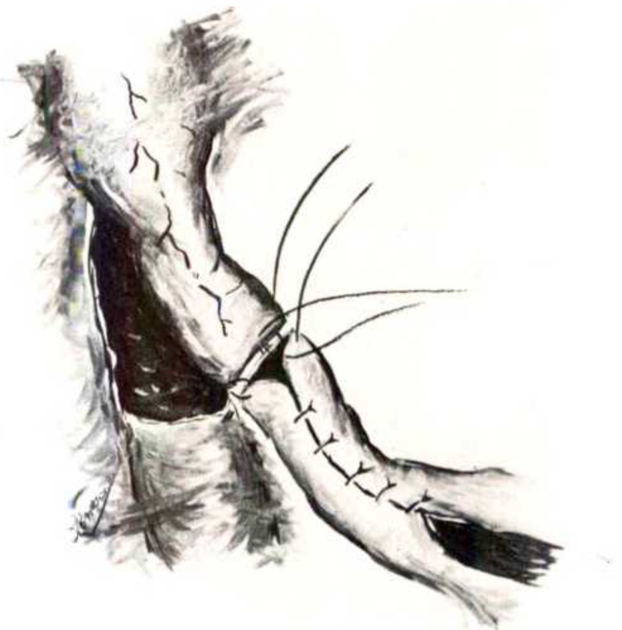

FIG. 2

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British Journal of Urology (1978), **50**, 57-61

Book Received

Hadfield, John and Hobsley, Michael (eds.): **Current Surgical Practice—Volume 1.** Edward Arnold, 1976, £14.00 net Boards, £6.95 net Paper.

Book Reviews

Complications of Urologic Surgery. Edited by Robert B. Smith and Donald G. Skinner. Pp. 502. Philadelphia: Saunders, 1976. £24.25.

In the preface of this book, the authors open with "expertise in the management of urological complications is derived from years of clinical experience. Resolution involves superb surgical ability and sound basic urological judgement, in addition to an inventive mind and an excellent bedside manner to instil patient confidence."

In the following 500 pages of this easily portable book, each of the 24 chapters is written by a world authority in the topic covered. The range is comprehensive, dealing with both medical and surgical complications that the surgeon may meet in urological practice, from infections and thrombosis (with up-to-date thinking on treatment) to complications of the more recently introduced surgical procedures like male anti-incontinence procedures and renal transplant surgery.

It is clear that the author of each chapter has a great depth of understanding of his subject and has taken care to describe at length the pros and cons of the placement of each stitch, and the suture material used, to avoid complications as well as the correction of them.

Clear drawings enhance the text, giving a greater understanding of the technical details where necessary. For those requiring further information on a subject, excellent up-to-date references are provided at the end of each chapter.

This book has tremendous appeal; it will be of great help to urological registrars during their training, and of considerable interest to experienced urological consultants.

J.R.H.

Scientific Foundations of Urology. Edited by D. Innes Williams and G. D. Chisholm. 2 volumes. Pp. xxviii + 848, with illustrations and tables. London: Heinemann, 1976. £38.00.

"Scientific Foundations—of urology?" Such was the mockery of not a few unenlightened clinical colleagues! Oblivious of the scepticism this book is true to its title, for barely a word about clinical, operative urology is to be found between its 4 covers. That is readily available elsewhere. Here, in 2 volumes, are the physiology, biochemistry, anatomy, epidemiology, immunology, pathology, endocrinology and physics of the urinary tract, the disorders that urologists treat and the therapeutic methods modern urology employs.

These fundamental facts and hypotheses are presented as 113 separate subjects with a single concise review of each written by a total of 53 international authors. Related subjects are grouped appropriately to provide as complete a picture as possible of a particular organ, system or discipline which in turn is easily identified in the table of contents. Volume 1 contains renal disorders, infections and calculi; Volume 2, the urogenital tract, oncology and the urological armamentarium. The large format with 2 columns per page, the controlled use of references and the absence of unnecessary illustrations are welcome. Unfortunately, a complete subject index is not provided in each volume.

Doubtless some of the authors will consider their contributions to be too brief. The editors have been ruthless. Some relevant subjects, much detail, many arguments and diversity of opinion have been sacrificed in the interest of brevity. If each author had been allowed full rein there could have been 10 volumes instead of 2. In the event we are presented with an encouraging example of good editorship. This is how a large poly-faceted multi-author text should be compiled, for despite its title it is eminently readable; a book to be kept at home rather than in the library; a book to be used frequently, though time be scarce, to refresh the lapsing memory with information that is indeed the foundation of daily clinical urological practice. The combined cost of both volumes may seem high, but it is excellent value for money.

Urologists are frequently considered to be practitioners of a skilled medical craft rather than of a scientific discipline. Any such concept has been admirably refuted in these 2 volumes.

R.R.H.

Cystic Diseases of the Kidney. Kenneth D. Gardner. Pp. ix + 225. Chichester: Wiley, 1976. Price £13.00.

This book is a comprehensive multi-author review of the many different varieties of cystic disease of the kidney.

This subject which causes much confusion is well setout, reviewing all the many syndromes associated with renal cystic disease.

As inevitably in any multi-author textbook, the chapters are variable in quality but the general standard is high and the chapter on Clinical Features and Pathophysiology of Polycystic Disease in Man is particularly useful to practising clinicians.

Also of use to the clinician is the chapter on Extrarenal Manifestations of Cystic Kidney Disease, the extent of which considerably surprised the present reviewer.

It is a book which should be on the library shelf of every department of urology but in view of the prevailing economic situation is unlikely to find itself on the shelf of many individual urologists.

J.C.S.

Radiology and the Kidney. Edited by C. J. Hodson. (**Contributions to Nephrology**, Vol. 5.) Pp. vi + 86, 41 figures, 2 tables. Basel: Karger, 1977. $19.00.

This small book is primarily aimed at nephrologists. It consists of 3 papers by radiologists well known for their work in the radiology of renal diseases.

The first by Talner is called "Functional Aspects of Uroradiology". It is an account of recent progress in the physiology of excreted contrast media and practical applications of this in the technique and interpretation of excretory urograms. It includes discussion of the role of radiology in the investigation of ureteric obstruction, hypertension, renal infections and masses.

The second by Hodson, called "Radiology of the Renal Parenchyma", is largely a summary of what is now well known thanks mainly to the efforts of Hodson himself. He shows how by relating the renal parenchyma to the calyces, conditions such as chronic pyelonephritis, reflux nephropathy, back pressure atrophy, papillary necrosis and tuberculosis can be diagnosed. He also discusses the differentiation of cortex from medulla and the value of arteriographic patterns in renal disease.

In the third one, called "Radiology in Renal Failure", Sherwood describes the value of excretory urography and other procedures such as antegrade urography. He emphasises how it is usually possible to avoid retrograde studies.

The book will prove useful for anybody wishing to catch up with recent developments. To this end it provides a good supply of useful references.

W.S.

Advances in Nephrology. From the Necker Hospital, Vol. 6. Edited by J. Hamburger, J. Crosnier and M. H. Maxwell. Pp. xv + 474. Well illustrated. Chicago: Year Book Medical Publishers, 1976. £31.00.

This book is the sixth of a series which aims to give "authoritative and current information on important topics in nephrology". There is no attempt to be comprehensive or systematic although taking all volumes together the bulk of nephrology is covered. The editors have certainly been successful in their choice of contributors; the book is in general well written and easy to read. The chapters written by the French authors tend to be in less flowing English, but this does no more than remind us that the author is French and does not interfere with clarity.

As with all textbooks there is an inevitable delay between completion of the manuscripts and publication. This makes it difficult for the reader to decide whether new material was not known to the author at the time of writing or was known but not considered worthy of inclusion. The chapter by Professor Kerr and his associates overcomes this problem admirably by an initial statement giving the date at which the review was completed. Thus, we are able to add the new findings concerning the role of aluminium in dialysis, bone disease and dementia to his "state of the art October 1975" without confusion.

It is difficult to pick out chapters for special mention, since all have merit. Pollack's review of the treatments for lupus nephritis will be of great value to nephrologists faced with the problem of when to employ toxic immunosuppressive drugs in these patients. Buhler puts the value of measuring renin in essential hypertension into perspective and presents new evidence to guide the use of beta-blockers. Assher's coverage of the relationship of urinary tract infection and reflux to renal damage is brief but readable. Kerr, Hoenich and Frost have produced a chapter which gives a clear, comprehensive and well documented account of dialysis which is very comprehensible despite the technicalities.

In summary then the book is well written and, for a textbook, up to date with appeal mainly to nephrologists, but also with items of interest to the immunologist and endocrinologist. I suspect that at £31 it will be a library rather than a personal purchase, but for those who already have purchased volumes 1 to 5 the temptation to spend a little more to keep the project going is reminiscent of that other Anglo-French project Concorde.

R.W.

Handbook of Urologic Emergencies. Edited by R. Kessler. Pp. 154 with 50 illustrations. Flushing NY: Medical Examination Publishing Company. 1976. $10.00.

This book is intended for casualty officers and senior students dealing with urgent urological problems. The book's size and chapter length make it suitable for carrying in a coat pocket and reading in short spells. The chapters cover infection, renal colic, retention and other disorders as well as trauma. Each chapter ends with a list of references.

There are the inevitable differences of approach which strike the English reader of an American book. These include the emphasis on gunshot wounds in injury to the ureter and the recommendation of suprapubic aspiration as the standard initial management of acute retention. It is assumed that IV urography and even angiography are immediately available.

Since 6 contributors share 100 pages of text it is not surprising that chapters vary in approach and degree of detail. In 1 chapter the reader apparently needs to be told how to pass a catheter, yet in a later chapter he is given details of uretero-neocystostomy by the Boari flap.

The worst aspect of the book is the poor reproduction of X-rays, some of which do not show the features stated in their captions. One must criticise a chapter on GU haemorrhage which shows a list of investigations of haematuria headed by "clotting studies" and which gives the impression to the reader that cystoscopy is needed only when the IVU shows no bleeding source in the upper tract.

The chapter dealing with rupture of the posterior urethra gives the sort of clear and imperative account of management which is needed in a handbook for accident-room use even where there is no agreement among the experts. The chapter on scrotal masses could be read with profit by examination candidates and that on priapism is a useful summary, with references, of the treatment of a rare emergency where prompt, correct treatment may make a big difference to the outcome.

The book will be a useful addition to the casualty department bookshelf, but the practising urologist will find it to be of very limited value.

K.B.

Textbook of Adverse Drug Reactions. Edited by D. M. Davies. 1st Edition. Pp. xvi + 503. Oxford: Oxford University Press. 1977. £14.00.

There seems little doubt that this book will prove to be a standard text on an important subject. The explosive development of pharmaceutical science in the last 20 years, together with an increasing population of elderly patients who require multiple therapy and suffer the attendant hazards of drug interactions, presents the contemporary clinician with the growing challenge of iatrogenic disease. There is also the problem of drug interference in laboratory procedures to mislead the unwary.

This book fulfils a need for a reference source to aid the clinician in identifying adverse reactions to his own and other people's prescriptions and in interpreting potentially misleading results of laboratory investigations. Despite the 32 different contributors the book achieves a satisfactory unity of style; the text is scholarly and gives ample references for the academically inclined. The chapters divide the subject primarily according to body systems, but most doctors will enter the book through the 48 page index listing symptoms and drug names.

Inevitably the specialist will feel some dissatisfaction with the detailed aspects of his particular field—readers of this Journal for example may feel disappointed that the bladder is the subject of less than 1 page of text—but few patients nowadays have the courtesy to restrict their diseases and treatments to the field of interest of the doctor looking after them, hence the need for a balanced and wide ranging text. Altogether this is a most satisfying and serviceable book and one that should, in my view, be available to every out-patient department and health centre as well as in every medical library.

J.G.E.

The Year Book of Urology—1976. Edited by John T. Grayhack, MD. 1 Volume. Pp. 385. Chicago: Year Book Medical Publishers, Inc., 1976. £15.60.

This series is too well-known to require introduction, and once again one can admire Dr Grayhack and his associates for their industry in summarising such a wealth of material from the huge volume of urological literature. As we have come to expect, the summaries themselves are concise, readable and accurate, and illuminated from time to time by the editors. The selection of papers is inevitably arbitrary and gives wide coverage to every aspect of urology, with the exception, perhaps, of bladder physiology which does appear to be under-represented in view of the increasing interest in this expanding field.

A new and interesting addition is an introductory 65 questions for clinicians. Anyone who has read the current literature can answer them: perhaps most of us would be glad that we are not compelled to do so. At the same time, one wonders how many of these "answers" will remain permanently embodied in the corpus of surgical truth.

The Year Book series has its limitations and its critics, but so long as the present high standard is maintained, others will, like the reviewer, regard it as one of the most valuable publications of the year.

D.M.E.

Kidney Biopsy Interpretation. Edited by E. H. Jenis and D. T. Lowenthal. Pp. 285. Philadelphia: Davis. 1977. £25.00.

It is not to be expected that many practising urologists will hasten to buy a volume with the above title, but the evident demand for specialised texts of this kind emphasises the divisions which are appearing in histopathology. Many pathologists and surgeons will mourn the eclipse of the general pathologist, recognising albeit reluctantly that this is the price of progress.

The contents of this excellently produced volume exemplify the features which have made renal pathology a distinct subspeciality. Above all is the dependence on electron microscopy as a genuine diagnostic tool. The micrographs here are excellent both in choice and quality, and notable in the technically flawless low-power micrographs. Light microscopy and immunofluorescent illustrations are of equally high standard. This combination of 3 demanding techniques in examining a tiny sample, and the development of specialised clinical departments has forced specialisation in a traditionally conservative field of medicine.

The text is divided into sections on primary and secondary glomerular disorders, and each chapter has almost forbiddingly regular sections on synonyms, incidence, age and sex, pathogenesis, clinical findings, light microscopy, immunofluorescence, electron microscopy, treatment, prognosis and differential diagnosis. The writing is precise and condensed. The references are always pertinent and the method of presentation with suffixed reference numbers leaves the text easy to read. The type is of unusual size and clarity.

The potential readership will be largely confined to those making critical appraisal of renal biopsies and with electron microscopy and immunofluorescence available to them. In the United Kingdom this means major teaching nephrology centres. Such units are usually linked with transplantation, and most renal pathologists deal with needle biopsies of graft rejection. It is hoped that future editions of this excellent book will include this aspect of renal pathology.

A.M.

Pediatric Nephrology. Edited by J. Strauss. Volume 3. Current Concepts in Diagnosis and Management. Pp. xiii + 401 with 47 illustrations. New York: Plenum Press, 1976. £13.00.

This is the third publication based on a series of annual paediatric nephrology seminars sponsored by the Division of Paediatrics in the University of Miami School of Medicine. Thus it is not strictly a textbook and the subject matter is not arranged in a logical sequence. In order to obtain the greatest value from the book it is clearly necessary to read the preceding 2 volumes.

Perhaps a surgeon has no right to review a book on such a medical topic except in so far as to advocate (or not, as the case may be) its value to his surgical colleagues. This reviewer on finding himself on 1 occasion in the company of a number of distinguished nephrologists was surprised to learn that these specialists do not confine their interests solely to the nephron but include the urinary collecting and transport systems in their field as well. Perhaps the next seminar in Miami will cover these aspects of the urinary tract: the subsequent publication would be more likely to stimulate the interest of the paediatric urologist. This is not to infer that everything in this book is arcanely medical. For example, every paediatric urologist should be familiar with the pharmacological management of hypertension and the chapter on this subject is excellent: the indications for and the mode of action of the numerous agents available are lucidly explained so that order can be seen in what most surgeons probably find confusing. The treatment of chronic renal failure and its metabolic sequelae is another area in which the paediatric urologist should have more than a passing interest. Unfortunately the chapter on sodium homeostasis is of little value except to the renal physiologist but those on calcium and phosphate metabolism and parathyroid function are good; so are the chapters on dialysis and transplantation. The remaining material in the book, though undoubtedly of a high standard of scientific accuracy indicates to this surgeon, at any rate, that the paediatric nephrologist is an essential member of any clinical team that aspires to care for children suffering from urinary tract disease.

J.E.S.S.

Laparoscopy. Edited by Jordan M. Phillips. Pp. xxxviii + 366 with colour atlas, figures and tables. Baltimore: Williams and Wilkins, 1977. $55.00.

The editor and his board are to be congratulated on producing what is probably the best comprehensive text on laparoscopy in the English language. It follows the authoritative monographs of Doctors Raoul Palmer, Hans Frangenheim, Patrick Steptoe and Melvin Cohen—an international quartet of experts who give this publication their combined blessing.

As a technique, abdominal endoscopy had early beginnings in Europe and America but only sporadic use in gynaecology. Palmer, the "father figure", in 1946 developed the essentials of the method we now use, calling it "gynaecological coelioscopy". Enthusiasm for the renamed laparoscopy spread quickly to England and America. Once accepted in the United States the technique acquired a large following amongst gynaecologists, resulting in the formation of the American Association of Gynaecological Laparoscopists, with a membership of over 2000.

This text is essentially a distillation of the American experience over the last decade. It outlines in detail the instrumentation and operative procedures, the indications and contraindications, the dangers and complications, the anaesthetic requirements, the patient counselling and the legal implications associated with laparoscopy. The contributors are sensibly cautious in their approach to operative laparoscopy, erring on the side of safety. Nevertheless, sterilisation procedures and infertility investigations are given up-to-date coverage. Of interest to neophytes and service organisers are details of available equipment, its care and maintenance, together with proven systems of instruction, both personal and academic.

The format is excellent, the text interestingly written and the references are up to date. The illustrations of the basic technique might have been better defined and the excellent colour atlas would be improved by combining the caption with the photograph.

This work undoubtedly deserves a place on the library shelves of clinical departments of gynaecology, anaesthetics, general surgery, urology, gastroenterology, oncology, and as part of the personal collection of individual laparoscopists. "Better to look and see than wait and see" might be the maxim of this fine publication.

D.T.

Female Urinary Incontinence. Edited by S. L. Stanton. 1 Volume. Pp. 118. London: Lloyd-Luke (Medical Books) Ltd, 1977. £4.00.

This is 1 of the books we have been waiting for. The major growing point in urology is in the realm of bladder function, and the advances made in the last few years have established almost a new discipline, with its own language, and concepts far removed from those found in current textbooks. As a result, those who are interested in this field of medicine find it increasingly difficult to communicate with our colleagues who are not *au fait* with current trends of opinion. In a short, readable, clearly written monograph, Mr Stanton has summarised an enormous mass of material of tremendous complexity and has produced a clear account of the diagnosis and treatment of this particular dysfunction. In so doing, he has also laid to rest some of the nonsense that has gained credence in the past, and demonstrated the value of a scientific approach to a difficult problem. He also demonstrates that the bladder is not the preserve solely of the urologist, but demands the attention of those who will study its function whatever their basic background. The day surely has come when the urologist and the gynaecologist can meet with a common understanding.

In the present context, neurological disorders of the bladder require a fuller treatment, particularly with reference to the older woman, who presents a challenge which is not adequately discussed. One misses, too, the problems of detrusor/outflow imbalance leading to incontinence, which is often easily overcome by dilatation or urethrotomy.

This is not to detract from the present book which remains a refreshing review of a large area of incontinence, and leaves room for expansion in future editions. It will become essential reading for all those interested in the bladder, and act as a bridge to facilitate communication with our colleagues. Mr Stanton deserves our thanks and congratulations.

D.M.E.

Renal Medicine. Edited by R. Gabriel. Concise Medical Textbook. London: Bailliere Tindall, 1977. 1st edition. Pp. 286, 36 figures, 10 tables. £3.50.

This book is aimed at the student rather than the postgraduate working for a higher examination and if this is remembered then few criticisms can be levelled at it. The style is clear and practical problems encountered by students are dealt with.

There are some minor irritations, in particular, for me the use of kilo Pascales for blood pressure is premature and is made less understandable by the use of the old units of ml/min for GFR. The many spelling mistakes may not be the fault of the author but they do interfere with the enjoyment of the text.

In the interests of brevity I think that the author has allowed the content of the chapter on renal physiology to fall below the level most of us would expect our students to know. For example no mention is made of the role of the renal nerves in the control of renin secretion, nor does the possibility of the existence of a natriuretic hormone get a mention.

The chapter on hypertension is well written and clear in many respects but could confuse students in others. Thus benign and essential are taken to be synonymous in describing hypertension, hypokalaemia is defined as a serum potassium less than 2 mmoles, and the phentolamine test "should be performed" in patients in whom phaeochromocytoma is suspected.

I think that the dogmatic approach, which students usually like, is taken too far in places and may misguide the reader; for example, it is implied that uraemic pericarditis is regularly accompanied by the classical concave elevation of the ST segment on ECG whereas in practice this is unusual.

In conclusion this is a clearly written concise renal textbook which will be of value to students but will require supplementation by renal physiology from a less concise source.

R.W.

Conferences and Courses

Scanning Electron Microscopy in Reproduction

Los Angeles. 21 April 1978

This workshop will take place during the Scanning Electron Microscopy/1978 meetings sponsored by Scanning Electron Microscopy Inc. Papers will discuss studies of reproductive tract and gamete morphology and physiology relating to fertility and infertility with a special emphasis on potential applications in both clinical and experimental fields, and on correlation with conventional methods of observation. The workshop is being organised by Professor E. M. Eddy, University of Washington Medical School, Seattle and Dr K. G. Gould, Yerkes Primate Center, Atlanta, Georgia.

For further information apply to: Dr Om Johari, 1420B Volid Drive, Hoffman Estates, Illinois, 60194, USA.

First International Kidney Transplant Course

Barcelona. 24, 25 and 26 April 1978

This course is organised by the Department of Urology, the Renal Transplant Unit and the Department of Immunology of the "Hospital Clinico y Provincial".

Further information from: Dr J. Masramon, Department of Urology, C/Casanova, 143, Barcelona, Spain.

Abstracts of the Proceedings of the Urological Society of Australasia 30th Annual General Meeting, Perth, Australia, 1977

President: S. H. Watson (Perth)
Honorary Secretary: H. M. Learoyd (Sydney)
Editor: J. P. Maddern (Adelaide)

Indonesian Endemic Bladder Stones

By T. A. Taylor
Department of Urology, Royal Perth Hospital, Perth, Western Australia

A study conducted on the west coast of Sumatra into endemic bladder stones is reported.

Within this area, 42 of the 86 cases reported occurred in a coastal rural and fishing community called Pariaman. Sex incidence was 12:1 in favour of males while the peak presentation age was 2 to 4 years. These children presented with pulling of the penis. In 50 consecutive cases no stones were found in the upper tract. X-ray crystallographic analysis of stones showed the bladder stones to be composed of calcium oxalate in the form of whewellite and ammonium acid urate. Spot urine collections showed significantly raised urinary ammonia/creatinine ratio in the stone-forming children. Diet pattern was that of other endemic areas with low animal protein, high carbohydrate intake. Breast feeding to 6 months was common and some infants developed stones while still on the breast. All cases drank either from a well or river water supply. Diarrhoea prior to the stone episode was a common event. Ammonium ion is known to be a powerful flocculator of urate and it is felt that preceding acidosis associated with low phosphate dietary intake will increase urinary ammonium excretion and hence lead to ammonium acid urate flocculations. This may act as the nidus for endemic bladder stones.

Formation of Stone

By R. C. Bowyer
Department of Biochemistry, Royal Perth Hospital, Perth, Western Australia

There is increasing evidence to suggest that inhibitor substances in urine play an important role in stone formation.

These substances may exert their action on at least 2 stages of production:

1. the spontaneous precipitation of very small particles from concentrated solutions of mineral ions;
2. the growth and aggregation of preformed particles in concentrated solutions of mineral ions.

To assist in the study of recurrent calcium oxalate stone formers in the Perth region, the calcium oxalate crystal growth and aggregation test used by Professor Nordin's group in Leeds has now been set up.

Investigation of endemic ammonium urate bladder stone disease in Indonesian children has included a study of urinary factors inhibiting the flocculation of urate in the presence of ammonium ion. Urea, the major component of urine, has no effect, whereas phosphate exerts an appreciable influence.

An ultrafiltrate of normal urine retains almost the entire inhibitory effect of normal urine itself, indicating that molecules with molecular weights of less than 10,000 are responsible for inhibiting flocculation in the ammonium urate system.

The proposition that crystallisation phenomena in calcium oxalate and ammonium urate stone formation share a common aetiology was discussed.

Uric Acid Metabolism and Stone Formation

By Irving H. Fox
University of Michigan, Medical Center, Ann Arbor, Michigan, USA

Stones associated with disordered purine metabolism include uric acid, calcium, oxalate, xanthine, 2,8-D/Hydroxyadenine, cystine and oxipurinol, but only the first 2 types of stones are common. Uric acid calculi occur with an incidence of 0.01% in the normal population but with an incidence of 10 to 25% in gout. They comprise 5 to 10% of all calculi in the USA. The major mechanisms affecting the formation of uric acid calculi include the urine uric acid concentration and the urinary pH. Uric acid is very insoluble below pH 5.0 and the solubility rises with increasing pH values: 60 to 80% of uric acid is ionized between pH 6.0 and 6.5. An increasing serum uric acid concentration value or a rising urine uric acid excretion value are associated with an elevated incidence of renal calculi in gout. Therapy includes adequate hydration, alkalining urine to pH 6.0 to 6.5, allopurinol, dietary reduction of purine intake if this is excessive and local measures of lavage or surgery as necessary.

In the formation of calcium oxalate stones an elevated serum or urine uric acid in one-third of patients has been implicated as an aetiological factor. Explanations for this phenomenon have included heterogeneous nucleation of calcium oxalate by monosodium urate or uric acid, or attenuation of urine crystal growth inhibitors by excess urine uric acid. The impressive reduction of the incidence of calcium oxalate stones by allopurinol in patients with disordered uric acid metabolism—for which group Coe has coined the term "Hyperuricosuric Calcium Oxalate Nephrolithiasis Syndrome"—is of great therapeutic importance.

Factors in Recurrent Oxalate Stones

By J. G. Brockis
University Department of Surgery, Royal Perth Hospital, Perth, Western Australia

Recurrence of upper urinary tract calculi occurs in up to 75% of patients. The longer the period of review, the higher the percentage quoted. There are differences in the incidence of the 2 major stone types between Australia and the United Kingdom. Uric acid stones only account for 3% in the UK but make up 15% of stones in Australia. There are 2 groups of hypotheses relating to the formation of calcium stones. The intracellular theories as exemplified by Randall's plaques and Carr's concretions and the chemical theories of which there are 3 sub-sections: (*a*) the concept of a mucoprotein matrix on which crystals form; (*b*) the Pak-Nordin theory of deposition of crystals from saturated solutions; and (*c*) the crystallisation inhibition theories of stone formation, which attributes stone formation at least in part to the failure of stabilising substances in the urine to hold calcium salts in solution. A simple method of estimating the presence or absence of inhibitors was described. It employs the Vicat apparatus used by engineers for testing the setting of cement. We have found that plaster of Paris setting parallels results obtained with the more sophisticated crystal growth measurement technique using a Coulter counter described by Robertson and his co-workers.

Litholysis—the Dissolution of Calcium Oxalate Stones

By G. J. Heap
Canberra Hospital
D. D. Perrin
Australian National University, Canberra, Australian Capital Territory

Unlike calcium phosphate and uric acid, calcium oxalate is extremely insoluble in both acid and alkaline solutions. Fortunately calcium oxalate is soluble in chelating agents, the most favourable being ethylene diamine tetra-acetic acid (EDTA). Furthermore, this substance has been used widely in the treatment of poisoning, and its toxic effects are well known.

The clinical use of litholysis was pioneered by Timmermann and Kallistratos of Hamberg, West Germany, and their method was used in modified form in this series.

A ureteric catheter is passed 5 to 10 cm beyond the stone, and is anchored in position by a balloon catheter in the urethra. The solution of chelating agent is dripped slowly through the ureteric catheter at a pressure not exceeding 50 cm H_2O. The irrigating fluid is warmed to 38°C by a water bath. The fluid is maintained at pH 8 buffering it and by giving alkalis by mouth. Thrombin is added to the irrigating fluid to reduce bleeding. Oral chlorpromazine is given for sedation and relief of ureteric pain. This series consists of 4 male patients, each with a ureteric stone otherwise requiring ureterolithotomy. In 3 cases, the ureteric stones were dissolved in 140 to 200 hours. The fourth stone was the largest. It became decalcified and reduced in size from 10 × 13 mm to 7 × 10 mm. However, it failed to disappear completely and irrigation was stopped after 723 hours. Later the stone was removed surgically.

The only complication of importance was urinary infection in 1 patient with a neurogenic bladder.

This small series shows that small stones will dissolve but larger ones may not. Failure seems to be due to the presence of matrix material in the stone which prevents penetration of the stone by the chelating agent. When this limitation is overcome, it is probable that litholysis will have a place in the treatment of ureteric calculi in urological units.

Incomplete Staghorn Calculus Surgery

By R. B. Brown
Alfred Hospital, Melbourne, Victoria

A review of 42 cases of staghorn calculi managed non-surgically prior to 1965 revealed that 65% of the unilateral and 80% of the bilateral cases died within 5 years. This personal series of 57 staghorn calculus operations was performed on 45 patients with a minimum 5-year follow-up. All patients had intermittent or continual symptoms of pain and infection and all were infected.

The majority (84%) of kidneys functioned although almost all had some decreased cortical area. 9 patients possessed no radiological function but this was not accepted as an absolute contraindication to conservative surgery.

Extended pyelolithotomy of the Gil-Vernet type, together with 1 or more nephrotomy incisions, performed through a cortical scar, was the predominant operation of choice. 6 partial nephrectomies were performed and 3 pyeloplasties. The renal artery was clamped on 9 occasions and hypothermia was used on 8 occasions. 2 nephrectomies were performed. Postoperative nephrostomy drainage and irrigation was not used but considerable emphasis was placed on postoperative intravenous diuretic hydration.

The results of such surgery were assessed in terms of intravenous pyelogram changes, symptoms, postoperative urinary tract infection, residual calcification and new calcification growth. In general the results were satisfactory, particularly in terms of the improvement in renal function and relief of symptoms. There were no operative deaths but there were 2 uraemic deaths within the 5-year follow-up period. 17 out of the 57 kidneys were still left with postoperative calcified material. Over the next 5 years there was an overall 53% increase in this calcified material size, but in only 2 cases was a second operation advised. Of the 40 cases radiologically cleared of calcified material, 8 (20%) re-calcified over the 5-year period.

The importance of postoperative urinary tract infection in either creating new areas of calcification or increasing the size of postoperative residual areas of calcification, was illustrated. Of the 32 kidneys which remained clear of stone over the 5-year follow-up period, only 6% had detectable postoperative urinary tract infection, whilst 88% of the 8 re-calcified kidneys and 100% of the incompletely cleared kidneys had persistent postoperative urinary tract infection.

The use of Renacidin in the Management of Staghorn Calculi

By E. J. England
A. I. Low
Royal Perth Hospital, Perth, Western Australia

14 patients were reviewed who have been treated since 1972 in whom removal of a staghorn calculus had been supplemented by irrigation of the kidney with Renacidin. The patients comprised 13 females and 1 male, with an average age of 40, most of whom presented with recurrent proteus urinary tract infections.

The stones were removed by an extended pyelolithotomy of the Gil-Vernet type supplemented in most of them by multiple nephrotomies. Most patients received a 6-week course of an oral antibiotic, usually amoxycillin, supplemented by 10 days of an aminoglycoside, usually gentamicin, this latter commencing just prior to surgery. The criteria of Nemoy and Stamey were adhered to rigidly, irrigation was not commenced until it could be shown that no leakage was occurring and the infusion was ceased in the event of any pain, fever or urinary infection. Residual calculi were present in 8 patients following surgery while 6 patients had no residual calculi. 1 to 19 litres of Renacidin were infused over 1 to 8 days, the average being 9 litres per 4 days, and 5 of the 9 residual calculi were dissolved. Of the 3 that failed, the supply of Renacidin ran out in 1, the second had to cease treatment because of a high fever and the third had calculi outside the pelvi-calyceal system.

A total of 12 complications was found in 7 patients, among which chemical cystitis was seen in 4. 2 patients had fever during the infusion due to infected urine. 3 patients developed candida infection and 2 serious complications were in this group. 1 had a high swinging fever for some weeks postoperatively and a second patient who had candida isolated subsequently had episodes of anuria resolving spontaneously with the passage of a candida cast from her solitary functioning kidney. The third patient was not affected by her fungal infection.

8 patients have been followed for more than 12 months with an average of 25 months and 2 of these have recurrent stones. 5 patients have no stones and no infections since operation. 6 have been followed for less than 12 months and 1 of these has a residual stone and infection and a second has extracalyceal fragments. The other 4 patients are free of stones or infections. Overall, therefore, 3 out of 14 patients have definite residual or recurrent stones and a fourth has extracalyceal fragments.

In conclusion, some complications have occurred with Renacidin, notably 2 serious problems with candida infection. It is felt that this is a very worthwhile technique when some residual fragments remain; in most instances these can be dissolved by irrigation with Renacidin.

Anuria in the Paraplegic

By Peter S. Lawson
Austin Hospital, Melbourne, Victoria

4 cases of absolute obstructive anuria have presented to the Austin Hospital Spinal Injuries centre in the last 20 years. Evidence is presented to show the anuria is caused by obstruction of the intramural ureter by intense spasm of a neurogenic bladder associated with severe infection.

The key to the management of these patients is to recognise the site and nature of the obstruction. The first clue comes during catheterisation because the catheter appears to stop at the bladder neck although in fact, it is hitting the dome of a spastic bladder and unable to curl up. This is confirmed by ascending urethrography which shows a bladder capacity of about 10 ml. In the presence of these 2 features a diagnosis of intramural ureteric obstruction by bladder spasm can be made.

In the first 3 cases the ureteric orifices could not be identified at cystoscopy because of gross bladder distortion and upper tract drainage was required. In the most recent case it was possible to identify the ureteric orifices and pass retrograde catheters. The condition is shown to be fully reversible if recognised early and generally lasts about 3 days. Both upper motor neurone and lower motor neurone types of bladder dysfunction have been affected.

The Drug Treatment of the Unstable Detrusor

By Alastair G. S. Tulloch
Sir Charles Gairdner Hospital, Perth, Western Australia

33 patients with unstable detrusors were treated with drugs. All patients had been referred from gynaecologists; 14 had had previous vaginal surgery for urinary symptoms. Their ages varied between 14 and 79, with a mean age of 62. The diagnosis of unstable detrusor was made with a cystometrogram using a rapid fill water technique. The plan of treatment was to begin with propantheline bromide (Pro-Banthine) in a dose of 30 mg 4 times each day. The dose was then adjusted so that the patient took the maximum dose that she could tolerate. If the patient failed to respond to propantheline, the propantheline treatment was continued but salbutamol (Ventolin) was added in a dose of 4 mg 3 times each day. In some patients the cystometrograms were repeated on patients whose symptoms were improved while they were taking drugs, but although the cystometrogram curves were improved, they did not return to normal. If a patient had responded to treatment, the drugs were withdrawn after 3 months. In some patients the improvement in symptoms was maintained, but others required long-term support with drugs.

Of the original 33 patients, 20 responded to propantheline in doses which varied between 45 mg 5 times each day to 15 mg twice a day. Of those 20, 6 patients' symptomatic improvement was maintained, but 14 required long-term treatment. 13 did not improve on propantheline alone, but of those 13, 5 were symptomatically improved when salbutamol was added. However, in none of those 5 patients, was it possible to withdraw salbutamol and propantheline and maintain improvement. There were 8 total failures of drug treatment and 6 have subsequently been treated with controlled bladder hydrodilatation.

The Evolution of Bladder Function following Spinal Cord Injury

By A. I. Low
Royal Perth Hospital, Perth, Western Australia

A study has been undertaken on all complete and permanent acute spinal cord injury patients admitted since the beginning of 1975. There were 11 males and 1 female, 6 with cervical injuries and 6 with thoraco-lumbar. The patients were studied 1 to 2 weekly from the time of injury with a urethral profile, cystometry, rectal pressure, intrinsic bladder pressure, flow rate, volume voided and EMG of their external anal sphincter.

The results of the urethral profile studies confirmed that there was a tendency for this to rise in the first 6 to 7 weeks after which there was a plateau with a tendency to a further gradual increase. 3 subgroups were found. 2 patients had a low pressure to begin with and remained within this range. The second group of 4 patients commenced in the lower range and rose to the intermediate or high level, and a final group of 6 started in the intermediate to high range with a further increase. Profiles of the 6 thoraco-lumbar patients were mostly in the high pressure range whereas cervical injuries started in the lower range.

The return of detrusor function was variable but followed a standard pattern of little activity to begin with, followed by uncoordinated fluctuations, to be succeeded by uninhibited detrusor contractions which, in general, became of higher amplitude and longer duration. Most patients developed the typical fluctuating systolic type of contractions seen in upper motor neurone bladder lesions. Cervical lesions were more likely to have an earlier return of function than the thoraco-lumbar group.

Detrusor/sphincteric dyssynergy was found to be moderate or gross in most of the cervical lesions and less marked in the thoraco-lumbar patients.

6 of the 11 male patients have, to date, been treated by transurethral sphincterotomy. All 3 who have been followed sufficiently long have shown a definite return of pressure in this region despite an apparently adequate sphincterotomy with no rise on the profile to begin with, suggesting that either our method is inadequate or that some return of activity is perhaps inevitable.

Combined Pressure, Flow, EMG and X-ray Studies for the Evaluation of Neurogenic Bladder Disturbance: Technique and Results

By H. Madersbacher
Urologische Univ.-Klinik, Innsbruck, Austria

A set-up for combined pressure, flow, EMG and X-ray recording was presented. Efforts are undertaken to prevent artefacts by manipulation, instrumentation and by the investigation itself. To fulfil some of the above-mentioned criteria, our basic conception is to perform instrumentation and manipulation, away from the investigation site.

Instrumentation involves suprapubic puncture of the bladder with 2 I Catheters ("Medium", Bard^R), 1 for continuous bladder filling, the other for continuous recording of the intravesical pressure and the insertion of 4 wire electrodes into the pelvic floor, 2 usually into the anal sphincter and the others into the area of the external urethral sphincter, or just into the pelvic floor to achieve a qualitative random electromyography of the pelvic floor striated muscle. These steps are usually done under a short anaesthetic and under cystoscopic control, especially in children and in patients with hyper-reflexic bladders. The investigation itself takes place at least 12 to 24 hours later. The only manipulation immediately before the investigation is the insertion of a tube into the rectum.

To combine pressure, flow and EMG recording with voiding cystourethrography, we designed a plastic, radiolucent micturition chair, which is placed on a mobile shelf. The chair can be rotated on an axis so that antero-posterior, oblique and lateral views are easily possible.

Urinary flow and volume are recorded with the flowmeter described by v. Garrelts and Strandell (1972). The following parameters are recorded on an 8-channel polygraph Mingo 81 (Elema-Schönander, Sweden): intravesical pressure, intra-abdominal pressure, the EMG activity of the pelvic floor and the flow and volume curve of micturition. Simultaneously, voiding cystourethrography can be recorded and can be stored on a videotape, to give the necessary additional morphological information.

The value of the technique was illustrated by graphs from patients with various types of neurogenic bladder dysfunction.

The demonstrated technique, which is time-consuming, gives useful information in a selected group of patients, but is not suitable as a screening test.

Recto-Prostatic Fistula: A Report of 2 Cases

By Brian McGregor
Queen Elizabeth II Medical Centre, Perth, Western Australia

2 cases of recto-prostatic fistula in patients with carcinoma of the prostate were presented. 1 developed following the use of a Vim-Silverman needle for a transrectal prostatic biopsy, the other after transvesical prostatectomy. Both cases were managed conservatively with a period of indwelling catheter drainage and stilboestrol. 1 patient required a temporary colostomy. Complete healing of the fistula occurred in both cases.

Although transperineal prostatic biopsy is a procedure which carries less risk of infection, the risk of tumour fungation seems to be a more common complication than with transrectal biopsy. The use of the Franzen needle for aspiration cytology is a safer method of prostatic biopsy than transperineal or transrectal needle or punch biopsy.

The Place of Radioisotope Bone Scans in Carcinoma of the Prostate

By Brian McGregor
Queen Elizabeth II Medical Centre, Perth, Western Australia

50 new cases of carcinoma of the prostate were assessed before treatment by skeletal X-ray survey and radioisotope bone scanning in addition to the routine blood tests. Anaemia, raised ESR, elevated serum acid and alkaline phosphatase levels and the histological grade of the primary tumour, were useful indicators of bony metastasis. Skeletal X-rays alone were very unreliable and the acid phosphatase estimation by itself was accurate in only 50% of patients who had metastases. The estimation of bone marrow acid phosphatase has recently been shown to indicate bony metastases more reliably and at an earlier stage than the bone scan.

The bone scan is best reserved for screening patients prior to radical treatment or when there is difficulty in making a diagnosis.

Radiotherapy Treatment of Carcinoma of Prostate

By Z. Herzberg
Royal Adelaide Hospital, Adelaide, South Australia

A review was undertaken to analyse the results of megavoltage radiotherapy in the treatment of Stage B and C carcinomas of the prostate. Over the 5-year period to August 1976, 138 cases were referred for treatment to the Radiotherapy Clinic at the Royal Adelaide Hospital.

Of the 138 cases, 89 had radiotherapy as their primary treatment while 49 were referred after a period of previous therapy, *i.e.* radiotherapy was given as a second line of treatment. 23 of the 89 were also given concomitant therapy in the form of oestrogen or bilateral orchidectomy. Subsequent analysis showed that hormone manipulation in conjunction with satisfactory radiotherapy did not improve survival. Of the 66 cases who had primary irradiation alone, 40 remained clinically free of tumour within the observation period; 3 had evidence of local disease; 15 were alive with bony secondary deposits. Actuarial survival of 4½ years was 83% for Stage B and 52% for Stage C. It was of interest to note that of all 89 who had primary irradiation only 5 required further TUR.

The remaining 49 patients had a "secondary" form of treatment and the usual indication was loss of local tumour control with out-flow obstruction, haematuria or obstructed ureter. 3 had experienced cardiovascular complications of oestrogen.

When the 138 cases were reviewed together, 4½ year actuarial survival rate was 75.8% for Stage B and 46.7% for Stage C.

Tumour differentiation was examined with Stage C and an overall poorer survival for poorly differentiated or anaplastic tumours was noted with 4½ year actuarial survival of 37%.

Most patients experienced gastro-intestinal or genito-urinary irritation from radiotherapy. If only patients who sought treatment for relief of symptoms are considered, in the group of early complications occurring within 3 months of irradiation, 58 patients suffered with mild gastro-intestinal and 60 mild genito-urinary symptoms, all usually responding to simple symptomatic remedies. However, 2 cases had diarrhoea severe enough to warrant discontinuation of irradiation.

Late complications were uncommon with persistent diarrhoea and micturition disturbance in 3 and 2 cases respectively. There was 1 case of rectovesical fistula and another of rectal ulcer; both were managed conservatively.

Radiotherapy is a successful and reasonably well tolerated form of therapy for Stage B and C carcinomas of the prostate both as primary treatment and also to achieve local tumour control in those cases where other therapy has failed.

Combination Chemotherapy for Stage IV Carcinoma of the Prostate

By John D. Taylor
Fremantle Hospital, Western Australia

A pilot study of a well defined group of patients with Stage IV carcinoma of the prostate has been undertaken at the Fremantle Hospital.

The group consisted solely of patients with intractable bone pain due to metastatic tumour. Less than 5% of all patients with carcinoma of the prostate are in this category at any one time. All had prostatic biopsy and bone marrow aspirate proof of Stage IV carcinoma of the prostate.

Chemotherapy required careful control as the patients were very ill. Once a remission had been induced treatment was continued on an out-patient basis. All remissions occurred within 10 days. All 5 patients whose disease had escaped from stilboestrol control were treated with an induction course of cytotoxic drugs followed by a maintenance course. All are in remission. The 2 longest survivors commenced treatment 11 and 12 months ago. The induction therapy consisted of 6 courses of 5 fluoro-uracil 300 mg daily, cyclophosphamide 300 mg in 2 doses, vincristine 0.5 mg in 2 doses and methotrexate 205 mg once over a 5-day period. A 16-day period elapsed between courses. Maintenance therapy commenced 3 weeks later and was as follows: stilboestrol 5 mg daily, prednisone 40 mg daily and cyclophosphamide 100 mg twice weekly.

The dose of prednisone was gradually reduced to 15 mg a day. An explanation for the choice of therapeutic agents was given. This therapy should be undertaken in conjunction with a haematologist or an oncologist.

Secondary Neoplasms of the Genito-Urinary Tract

By D. I. Roberts
Launceston, Tasmania

Secondary neoplasms of the genito-urinary tract form 2 groups:

1. those arising from primary growths elsewhere;
2. those arising from genito-urinary primary growths.

The kidney is the fifth most common site for secondary metastasis. Bilateral involvement occurs in 50% of cases. Renal metastasis is present in 20% of cases of bronchial carcinoma. Clinical detection is difficult because haematuria is uncommon.

Metastatic ureteric tumour may involve the adventitia, the muscle wall or the submucosa and causes obstructive symptoms.

Bladder metastases are uncommon, accounting for less than 2% of all bladder tumours. Direct tumour extension to the bladder is more frequent and may occur late, especially in cases of carcinoma of the rectum and cervix. Leukaemic infiltration of the bladder can occur and causes haematuria.

Secondary involvement of the prostate is rare but direct prostatic involvement can occur years after resection of recto-sigmoid carcinoma—possibly predisposed to by the destruction of Denonvilliers fascia at the original operation.

The most important urethral secondary deposit is that associated with bladder carcinoma. 12% of patients undergoing cystourethrectomy for bladder carcinoma show either carcinoma *in situ* or epithelial atypia in the urethra. Urethral fulguration of secondaries encourages blood borne dissemination.

Nodules in the cavernosa are the commonest form of penile metastasis and may cause urethral bleeding or retention.

Secondary neoplasm of the testis may occur with lymphoma, carcinoma of the prostate or lung, but is rare.

Treatment only occasionally effects a long-term remission but worthwhile palliation can be obtained in selected cases of secondary neoplasm of the genito-urinary tract.

Urine Cytology in Current Hospital Practice

By David Golovsky
Repatriation General Hospital, Concord, Sydney, New South Wales

189 patients had urines examined for malignant cells over a 12-month period. Of 97 patients with haematuria, 5 showed malignant cells in the urine and a further 10 were reported as atypical. 4 of these 10 subsequently had bladder tumours removed. Carcinoma was subsequently found in 9 cases where malignant cells were not seen. In

3 cases a tumour could not be found where malignant cells were reported in the urine. Higher grade tumours were more likely to have cells exfoliate and thus were easier to pick up in the urine.

In following up cases of proven past transitional cell carcinoma of the bladder difficulty was again encountered in finding malignant cells from a well differentiated tumour recurrence. 9 out of 13 urines from patients with analgesic disease showed either malignant or suspicious cells in the urine. It is suggested that urine cytology is mandatory in the routine follow-up of all cases of analgesic nephropathy.

The Long-Term Renal Outlook following Ileal Conduit Diversion

By Durham Smith
Royal Children's Hospital, Melbourne, Victoria

Up to December 1975, 322 ileal conduits have been performed in children, 278 for myelomeningocoele and 44 for bladder exstrophy, epispadias, sacral agenesis, pelvic malignancy and obscure neurogenic bladder.

The long-term analysis is of follow-up at 5 years, 5 to 10 years and 10 to 20 years after diversion, on the basis of serial IVPs, conduitograms, urine collections and ileal biopsies.

(1) The most important parameter in prognosis is the state of the upper tract at the time of the diversion. When diversion is performed while the upper tract is normal, 7% show deterioration at 5-year follow-up, 10% at 10 years and 23% more than 10 years later; if diversion is performed in an already abnormal system, further deterioration occurs in 16%, 20% and 45% respectively at the same intervals. Only 15% improve and in the remainder the changes remain static and thus constitute a continuing renal risk, *i.e.* late diversion does not often reverse the damage. Early diversion before renal deterioration is therefore advocated.

(2) At 10 to 20-year follow-up, 10% have died, 10% are hypertensive and 5% have calculi.

(3) Over the whole period, stomal stenosis occurred in 7% (12% in the over-10 year group); uretero-ileal stenosis in 2%; pyocystis in 30% (mainly in the early years); appliance problems in 20% (mainly early).

Deterioration in conduit patients may possibly be less in colonic than ileal conduit, perhaps due to an antireflux technique possible in the former.

Idiopathic Retroperitoneal Fibrosis

By R. E. Williams
General Infirmary, Leeds

34 patients have presented at the Department of Urology, Leeds, in the years 1956-76, with idiopathic retroperitoneal fibrosis. The aetiology of the condition has been discussed with particular reference to the action of Methylsergide.

Attention has been drawn to the other drugs which may produce this fibrosis, including LSD, Methyl Dopa and analgesics. In 29 of the patients, primary treatment was by ureterolysis which was successful in all but 1 case. In 2 patients a nephrectomy was done and another case presented at post-mortem. 3 patients were treated by steroids: 1 because a previous laparotomy had been done, 1 because of gross obesity and 1, following unilateral ureterolysis. It is recommended that in bilateral ureteric obstruction, the side more severely affected should be dealt with by ureterolysis, a large biopsy obtained to exclude the possibility of malignant infiltration, and the ureter freed. The patient may then be treated with steroids and the recovery on the contralateral side can be expected. It is recommended that the approach to the ureters should be extraperitoneal rather than transperitoneal.

The Management of Ureteroceles in Children

By Durham Smith
Royal Children's Hospital, Melbourne, Victoria

Over a 20-year period 95 ureteroceles in 82 patients have been managed by a variety of techniques, representing our gradual understanding of the pathology of these lesions.

A wide range of associated parameters influences the choice of treatment in individual patients, *e.g.* the type and site of ureterocele, the duplex or single nature of the subserving kidney, renal function of each renal segment, the presence of reflux in the orthotopic ureter, etc.

Simple transurethral resection or open meatotomy of the ureterocele has failed in 50% of patients because of subsequent infection or reflux.

Unroofing of 27 ureteroceles with varying procedures to the ureters (re-implantation, uretero-ureterostomy, ligation of ectopic, etc.) but retaining the subserving hemi-kidney, failed in 16 cases, requiring subsequent procedures.

Conversely, excision of the subserving kidney (hemi- or total nephrectomy) but retaining the ureterocele, resulted in complications in 50%.

Total excision of ureterocele, ureter and subserving hemi-kidney, if the latter is grossly dysplastic, or total excision of ureterocele and re-implantation of ureter if the kidney is sound, provided the only consistently good results.

The complicated relationships between the various adverse factors, the fate of re-implanting both the orthotopic and ectopic ureters and the operative technique in excision and in re-implantation, were described and particular reference made to the difficult caeco-ureterocele.

Male Infertility in Relationship to Immunofluorescent Staining of Testicular Tissue*

By T. A. Taylor
Royal Perth Hospital, Perth, Western Australia

The possibility of an auto-immune reaction developing against spermatogonium as a cause of male infertility is an attractive hypothesis. Spermatogonia and the basement membrane of seminiferous tubules mature between the ages of 5 and 9 years—long after immunological tolerance has developed in the foetus. Of 18 patients reported, 12 were azoospermic and 6 oligozoospermic on seminal analysis. Comparison between the seminal analyses, testicular biopsy, and immunofluorescent staining of each patient was determined.

All oligozoospermic patients showed staining of the basement membrane in both testes, with IgG and C3 predominating except for 1 case. Of the azoospermic patients, these showed maturation arrest; only 2 out of 9 showed staining. 1 of these patients was a diabetic, aged 31, on insulin, and it was felt that his staining characteristics may have been related to his diabetes rather than to his infertility. 2 patients with germ cell aplasia showed granular deposits of IgG, IgM, C3 and less by C1q on the walls of blood vessels.

In conclusion, it was felt that the oligozoospermic patients may have inadequate development of their basement membrane as an immunological barrier secondary to viral infection or a cross reaction with a viral or bacterial antigen. The azoospermic patients with maturation arrest who had no immunofluorescent staining may have an obstructive aetiology as the basis of their infertility.

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* This work was undertaken in the General Infirmary, Leeds, in conjunction with the Department of Immunology, University of Leeds.

Glycine—a Safe Irrigating Fluid

By Malcolm Drummond
Royal Prince Alfred Hospital, Camperdown, New South Wales

Over the last 5 years, a number of deaths in association with transurethral resection of the prostate (TUR) have been reported to the Special Committee Investigating Deaths under Anaesthetics in NSW.

Most have been elderly with a previous history of cardiac and/or renal disease. Deterioration in cardiovascular status developed after 25 to 40 min of resection; the terminal event has been pulmonary oedema; autopsy has not revealed evidence of myocardial infarction; and in all cases water was used as an irrigating solution.

The problems associated with TUR have been well documented; Creevy has shown a 15-fold increase in plasma haemoglobin when water is used as irrigation; Madsen and Naber have demonstrated rapid and large fluid absorption when the pressure in the prostatic fossa rises above 55 cm water; Ascheim has demonstrated hyponatraemia following fluid absorption.

A prospective study has been carried out using isotonic glycine as irrigating fluid together with an irrigating fluid pressure of 45 cm glycine. 20 patients were studied, and blood samples were taken before resection and at 15 min intervals during resection and 15 min after the completion of the resection.

Estimation of serum sodium potassium and chloride and serum osmolarity and serum iron were carried out on each sample. The serum iron estimation was used to detect haemolysis, as variations in plasma haemoglobin are reflected in the serum iron.

The results failed to detect any significant variation in the parameters studied when the pre- and postresection samples were analysed. It was concluded that in a small series of resections, in which those factors, known to contribute to the incidence of intravascular haemolysis and hyponatraemia, were controlled, there was no biochemical disturbance.

The Adult Enuretic

By W. Keith Yeates
Newcastle General Hospital, Newcastle upon Tyne

The normal functional bladder capacity will accommodate a sleep's output of urine. There are 2 basic mechanisms of active nocturnal incontinence: (*a*) The combination of the functional bladder capacity being reached during sleep, and the failure of reception of arousal by the resulting stimuli; or (*b*) Unconscious wilful micturition. There is little evidence of a combination of (*a*) and (*b*).

Recognition of the type is essential in planning treatment. Type (*a*) usually has demonstrable uninhibited contractions. It requires enlargement of the functional bladder capacity. Adult enuretics rarely respond to the drugs which are so effective in children. Operative enlargement of the functional bladder capacity is the only rational approach for a potentially lifelong disability. Whenever possible surgical procedures should affect only the bladder and therefore are preferable to neurosurgical procedures.

Transection of the bladder was performed based on the concept of dividing the nerves supplying the bladder vault. The results in 44 cases were: 16 of 26 men were completely cured of their nocturnal incontinence, and a further 8 were wet only 1 night a week, in contrast to there being 12 who were wet nearly every night before operation. 8 of 18 women were completely cured of their nocturnal incontinence, and a further 6 were wet only 1 night a week in contrast to 10 who were wet most nights before operation. 3 of the women continued to be wet every night. 31 out of 41 had normal frequency post-operatively compared with 26 out of 41 who had very marked frequency pre-operatively. There has been no deterioration in the results of the patients followed from 1 to 7 years.

The alternative procedure of prolonged over-distension under epidural anaesthesia is reported to be excellent in some cases, but overall the results seem to be less effective than transection. The rational approach to the patient with both night and day symptoms would appear to be over-distension initially and transection if this fails or the symptoms recur.

Patients with only nocturnal incontinence (Type (*b*)) usually have stable bladders. A few cases have been managed successfully with the new antidiuretic DDAVP which will produce anuria for about 6 hours, and appears to have no side effects.

Male Infertility—a Critique and some Concepts

By W. Keith Yeates
Newcastle General Hospital, Newcastle upon Tyne

There are 3 aspects of male infertility of particular interest to the urologist—its recognition—the varicocele and obstructive azoospermia.

Ordinary semen analysis is an outstandingly unsatisfactory investigation. There is little or no difference in the sperm counts in over 80% of infertile marriages where the wife is apparently normal. Opinions on normal sperm morphology differ widely. Motility is difficult to grade. The cervical mucus acts as a physiological filter. The most rational assessment would therefore appear to be a quantitative cervical mucus invasion test.

Only 50% of varicocele operations resulting in pregnancy have detectable improvement in the usual parameters and successful cases have had normal mucus invasion ability pre-operatively (Nilsson, 1976). Therefore the operation must be affecting factors which act beyond the cervical mucus such as the enzymes in the sperm head, with incidental improvement in motility and/or morphology in 50%. The reduced success of operations for varicocele by delaying operation until there has been infertility for 2 years is a measure of the natural occurrence of pregnancy. A critical re-appraisal of the reasons for the apparent success of varicocele operations in infertility is required.

An international survey of the results of vasoepididymostomy for obstructive azoospermia clearly shows that they depend on whether or not there is an infective cause. More than 40% of my cases of obstructive azoospermia have a definite history of bronchiectasis in childhood (the Berry-Perkins-Young Syndrome).

All had active sperms in the head of the epididymis above a collapsed upper body of epididymis. Actual obstruction has not been demonstrated. It is not possible to show if they are very mild cases of cystic fibrosis. There is no common deficiency of cilia in the epithelia of the respiratory and genital tracts as demonstrated by nasal cytology. Strips of tunica albuginia showed no contraction on electrical stimulation. It is speculated that the failure of vasoepididymostomy in these cases is because the primary deficiency is one of propulsion by the muscle of the tunica albuginia.

The most striking feature of this tricentenary of the first observation of a human spermatozoon is the continued lack of understanding of most of the causes of male infertility.

To Be or Not to Be Accepted for Publication

By W. Keith Yeates
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Publication of clinical information has to be restricted to the quantity and quality the subscriber is willing to pay for. The size of a journal is therefore limited and the material to be published has to be carefully selected. The decision to accept or not to accept a paper is relatively easy in 20% at each end of the scale, but 60% are in the balance and of these a half will eventually be accepted. There are 2 main aspects of a paper—the message and its presentation. The message must be urologist-orientated and it must be new or nearly new—and it certainly should appear to be worthwhile. Urological messages are of infinite variety but fall roughly into certain categories. In order to transmit the message to the best advantage the presentation in each of these categories has to be rather different. These categories with outlines of the presentations required are to be found in an apparently obscure part of the *British Journal of Urology* headed Instructions to Authors.

The most desirable paper has a single, new, worthwhile message, briefly, simply and clearly presented. The most frequently rejected paper is a retrospective survey describing a large number of features superficially.

All papers are referred to an Adviser or Referee. The satisfactory Adviser is able not only to give a clear opinion as to whether a paper should or should not be accepted, but also to make helpful comments which will be appreciated by the author even if his paper is rejected. The questionnaire sent to Advisers by the Editor is available to all potential contributors on request, from the editorial office.

About 80% of papers acceptable for publication have to be returned to the authors for adjustment mostly due to their not having complied with requests in Instructions to Authors.

Urological Implications of Food Refining

By N. O. K. Gibbon
Sefton General Hospital, Liverpool

The realisation that food refining (of cereals, sugar beet and sugar cane), leads not only to general overconsumption but also to dietary deficiency of fibre and other substances (Cleave and Campbell, 1969) has proved to be the greatest stimulus to clinical research since the germ theory. Attention is drawn in this paper to 2 of the most obvious urological implications:

(1) *Urinary Tract Infection.* The common ascending infection in women may well be related to the changes in the bacterial flora of the colon which are known to occur as a result of stasis and a surplus of soluble food residues. This offers the possibility of primary prevention as opposed to the secondary and tertiary measures now in vogue (perineal hygiene and postcoital voiding respectively).

(2) *Renal Calculus.* The modern epidemic of renal calcium stones in the "developed" countries is closely associated to hyperabsorption of calcium and response to a reduction in the intake of dairy produce is disappointing. The condition is possibly related to phytate deficiency (Widdowson, 1969). The present author has not failed so far to reduce the urinary calcium levels to normal in such cases by a change from white to wholemeal bread, though of course to demonstrate the effect on recurrent stone formation will require a much longer follow-up.

As attention has recently been re-focused on the role of oxalate it is worth remembering that this is a by-product of carbohydrate metabolism and of the glycine synthesis which follows the wastage of bile salts accompanying a low fibre diet.

The Neuropathic Urethra

By N. O. K. Gibbon
Sefton General Hospital, Liverpool

Watkins (1936) showed that in cauda equina lesions there is membranous urethral obstruction despite flaccidity of the external sphincter. Such patients often void better lying down and the increase in urethral resistance known to be associated with sitting up (Gibbon, 1973), is due to smooth muscle activity (Abel *et al.*, 1974). Shamsunder *et al.* (1977) have demonstrated a similar abnormal postural increase in membranous urethral resistance in injuries above the sacral segments. This has a large smooth muscle component which seems to be implicated in cases of failed "external sphincterotomy". Furthermore, some women liable to retention, show a similar urethral response, without any obvious neuropathy.

Failure to explain these findings on a reflex basis has led to speculation about the possibility of a humoral mechanism. The plain muscle of the urethra may become supersensitive to circulating catecholamines in much the same way that the denervated detrusor reacts abnormally to cholinergic drugs. Preliminary experiments using thigh cuffs in the supine patient have resulted in changes in the urethral pressure profile. It seems possible that further investigations along these lines might open up new aspects of the pathophysiology of the urethra which could be of practical importance not only to the paraplegic but also to some apparently healthy patients with voiding difficulties.

Serum Testosterone Levels Present in Venous Samples Taken at Operation from the Testicular Veins of the Varicocoeles

By Alan Fortune
Fremantle Hospital, Perth, Western Australia

A comparison of the testosterone levels in the internal spermatic vein of 26 patients with varicocoele and 4 normal patients, and the relationship with the testicular histology between elevated serum was made.

Blood samples were taken from the right antecubital vein and from the left testicular vein. Bilateral testicular biopsies were done on the varicocoele group and were examined to assess whether there was any correlation between those patients in whom deteriorative changes were demonstrable, and the level of serum testosterone from the left testicular vein. As normal controls series of 4 patients, had blood taken from the left testicular and right antecubital veins at the time of repair of an inguinal hernia.

From the findings obtained there was a significant elevation of serum testosterone from the testicular veins of those patients in whom a varicocoele was present. In 7 patients demonstrable testicular pathology was observed.

With respect to testicular pathology, no correlation could be established between the level or degree of elevation of the serum testosterone from the testicular vein and the presence of altered testicular structure.

CURRENT UROLOGICAL LITERATURE: SELECT BIBLIOGRAPHY[1]

The List of Current Urological Literature is now arranged to correspond to the order in which papers are published in the *Journal, i.e.* in anatomical order beginning with papers on the kidney.

A general section is included at the end.

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Conversion Table—SI Units

Old Units			Conversion factor Multiply by:		S.I. Units	
Constituent	Normal range	Units	Old to New	New to Old	Normal range	Units
Venous Blood						
Albumin	3·5–5·5	g/100 ml	10	0·1	35–55	g/l
Bicarbonate (total)	24–30	mEq/l	1	1	24–30	mmol/l
Bilirubin	0·1–0·8	mg/100 ml	17	0·059	2–14	μmol/l
Calcium	8·6–10·5	mg/100 ml	0·25	4	2·15–2·65	mmol/l
Chloride	100–107	mEq/l	1	1	100–107	mmol/l
Cholesterol	140–240	mg/100 ml	0·026	38·5	4·0–6·5	mmol/l
Creatinine	0·6–1·4	mg/100 ml	88	0·0114	55–125	μmol/l
Glucose	65–95	mg/100 ml	0·056	18	3·5–5·5	mmol/l
Iron	110–130	μg/100 ml	0·18	5·6	circa 20	μmol/l
Magnesium	1·4–1·8	mEq/l	0·5	2	0·70–0·90	mmol/l
Phosphate	2·5–4·5	mg/100 ml	0·32	3·1	0·8–1·4	mmol/l
Potassium	3·8–5·2	mEq/l	1	1	3·8–5·2	mmol/l
Protein (total)	6·5–8·0	g/100 ml	10	0·1	65–80	g/l
P.B.I.	3·75–7·5	μg/100 ml	79	0·0127	300–600	nmol/l
IgG	500–1600	mg/100 ml	0·01	100	5·0–16·0	g/l
IgA	125–425	mg/100 ml	0·01	100	1·25–4·25	g/l
IgM	50–180	mg/100 ml	0·01	100	0·5–1·8	g/l
Sodium	136–149	mEq/l	1	1	136–149	mmol/l
Transferrin	150–300	mg/100 ml	0·01	100	1·5–3·0	g/l
Triglyceride	60–140	mg/100 ml	0·0113	88·5	M2·0 P < 1·5	mmol/l
Uric Acid	2–7	mg/100 ml	0·06	16·7	0·1–0·4	mmol/l
Urea	15–40	mg/100 ml	0·17	6·0	2·5–6·5	mmol/l
Arterial Blood						
Base Excess	−3–+3	mEq/l	1	1	−3–+3	mmol/l
PCO_2	32–46	mm Hg	0·135	7·5	4·5–6·0	kPa
PO_2	80–100	mm Hg	0·133	7·5	10·5–13·5	kPa
Urine Outputs/24 hr						
Calcium	200	mg	0·025	40	5	mmol
Creatinine	1–2	g	8·8	0·113	9–18	mmol
5H1AA	3–17	mg	5·23	0·19	16–90	μmol
Inorganic P.	1000	mg	0·032	31	30	mmol
Magnesium	100	mg	0·041	24	4·2	mmol
Potassium	70	mEq	1	1	70	mmol
Protein	< 0·05	g	1	1	< 0·05	g
Sodium	200	mEq	1	1	200	mmol
Urea	25	g	17	0·06	400	mmol
Uric Acid	500	mg	0·006	167	3·0	mmol
VMA	< 7	mg	5·05	0·2	< 35	μmol

February 1978 Volume 50 Number 1

Contents

1 Perfusion Characteristics of Preserved Canine Kidneys subjected to Warm Ischaemia
V. K. Modgill, P. A. Wiggins and G. R. Giles

8 Control of Bleeding after Renal Biopsy with Epsilonamino-Caproic Acid
E. Savdie, J. F. Mahony and B. G. Storey

12 Ultrastructure and Pathogenesis of Human Urinary Calculi
M. Spector, N. M. Garden and S. N. Rous

16 Transient Ureteric Dilatation in Neonates with Imperforate Anus: a Report of 4 Cases
A. M. K. Rickwood

20 Urodynamics in Benign Prostatic Hypertrophy
R. M. Anikwe

25 Methyl Cholanthrene and Cadmium Induced Changes in Rat Prostate
R. Scott and E. Aughey

29 Prednimustine Therapy for Advanced Prostatic Cancer
R. Catane, J. H. Kaufman, S. Madajewicz, A. Mittelman and G. P. Murphy

33 The Measurement and Interpretation of Urethral Pressures obtained by the Method of Brown and Wickham
P. H. Abrams, S. Martin and D. J. Griffiths

39 Cordopexy: a New Approach to the Undescended Testis
S. K. Saha

43 The Testes after Torsion
Torben Krarup

47 Controlled Clinical Trial of Arginine for Infertile Men with Oligozoospermia
J. P. Pryor, J. P. Blandy, P. Evans, D. M. Chaput De Saintonge and M. Usherwood

Single Case Reports

51 Bilateral Pelvic Ectopic Kidneys
J. Fischelovitch and J. Jancu

52 Intimal Tear, cause of Transplant Failure
Zvi F. Braf and Ada Horowitz

53 An Unusual Case of Cavernostis
C. R. R. Corbett

54 Severe Hypertension following Traumatic Renal Infarction
B. J. Abel and J. H. Kennedy

Points of Technique

55 An Instrument for Intrarenal Irrigation
Bruce S. Pearson

56 Method of Mobilising the Adherent Obstructed Ureter
Bruce S. Pearson

57 Book Received

57 Book Reviews

62 Conferences and Courses

63 Abstracts of the Proceedings of the Urological Society of Australasia, 30th Annual General Meeting, Perth, Australia, 1977

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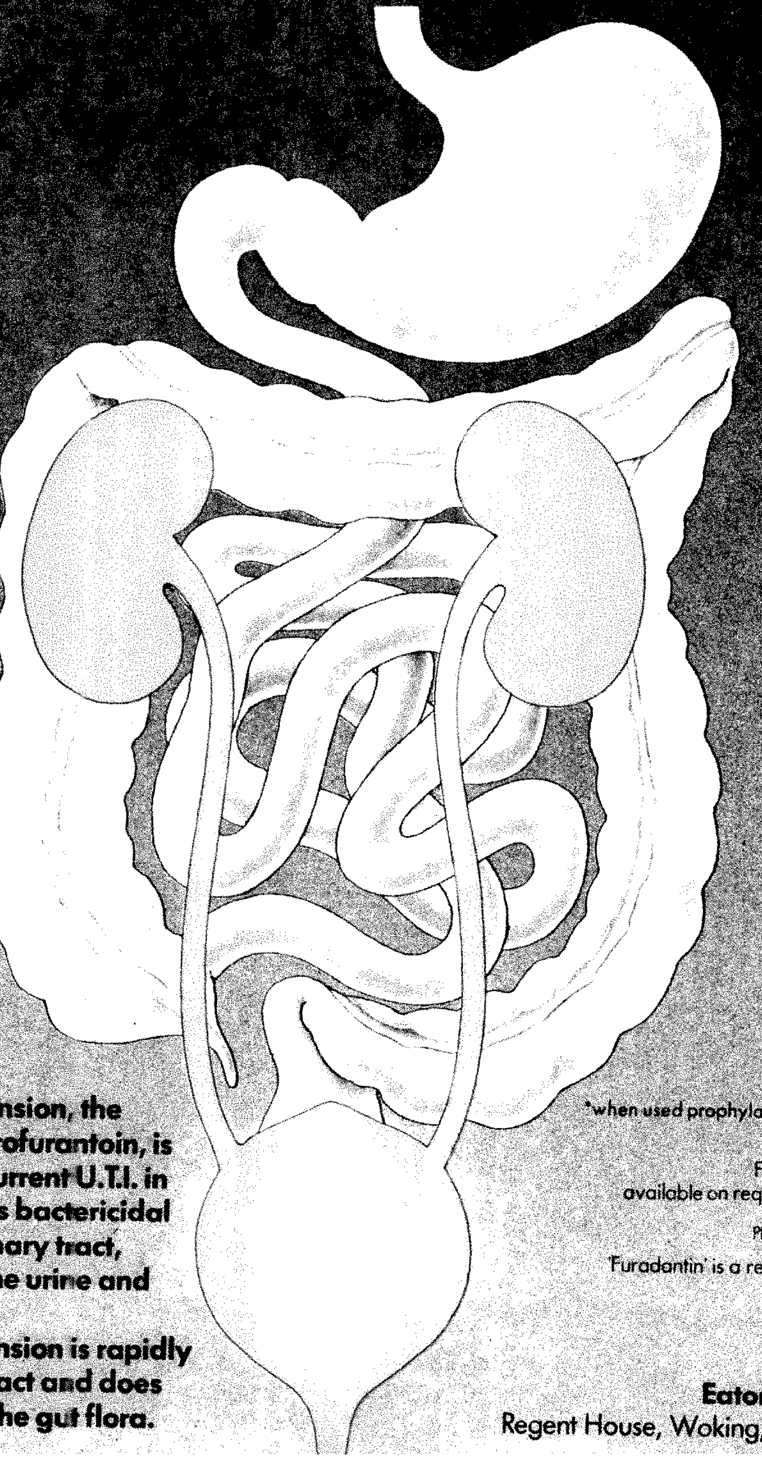

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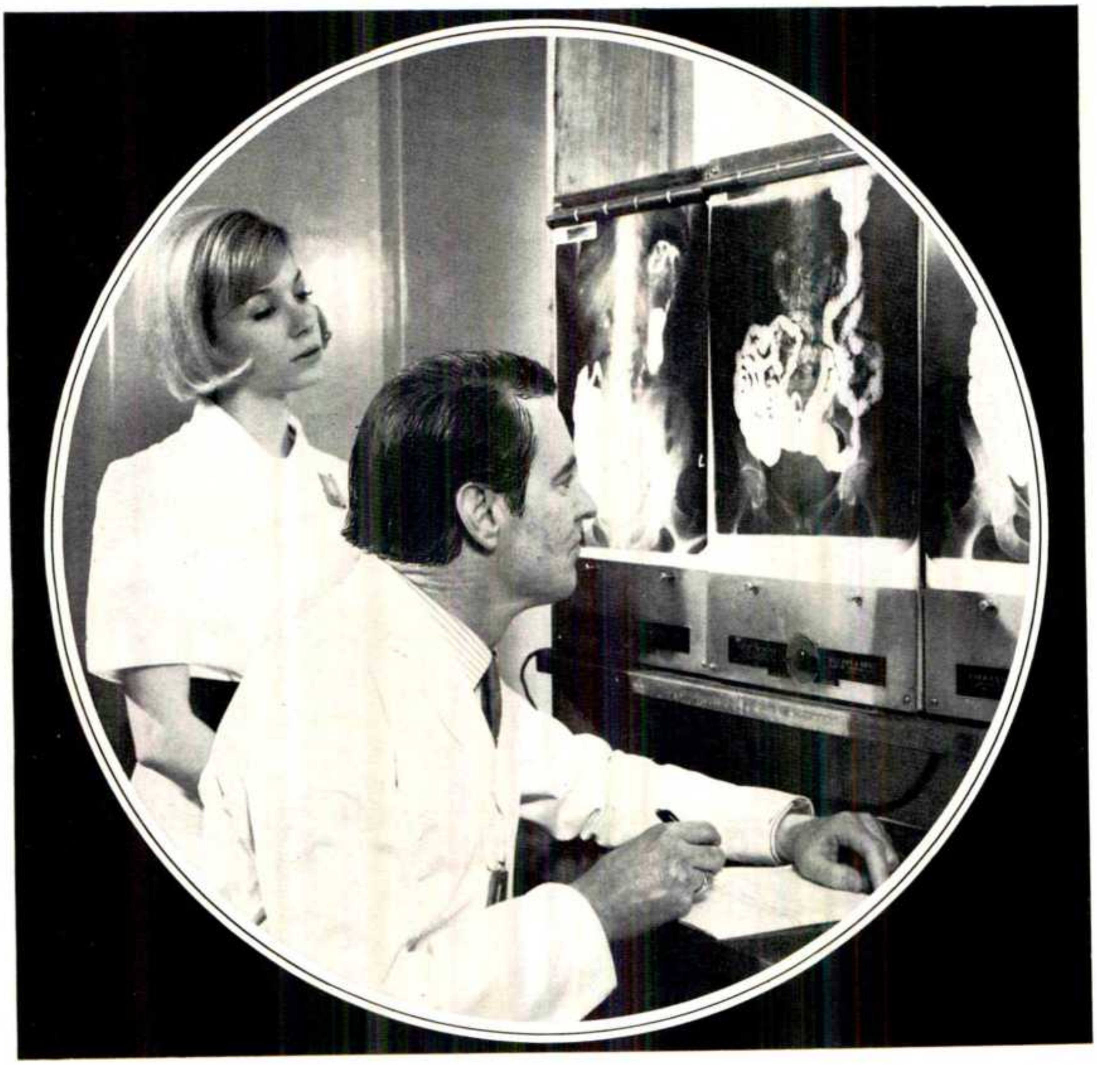

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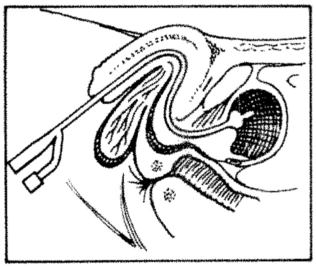

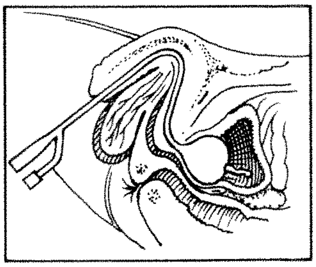

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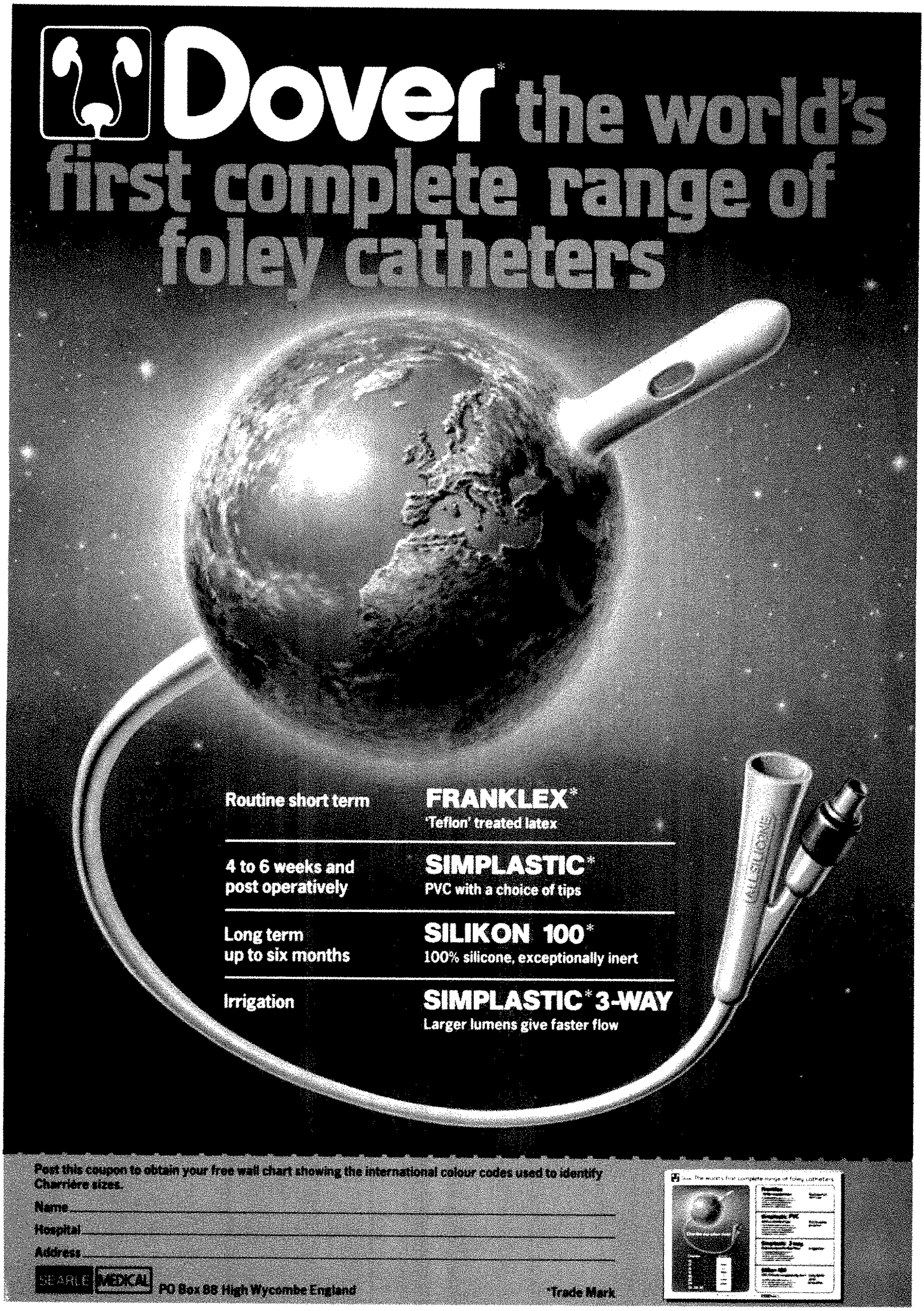

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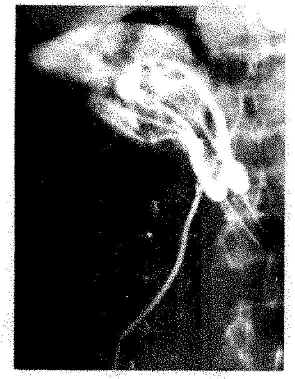

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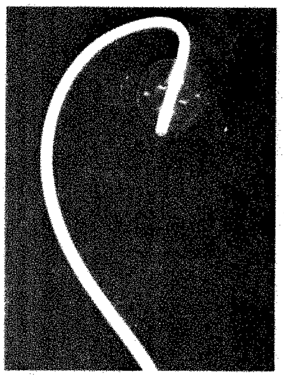

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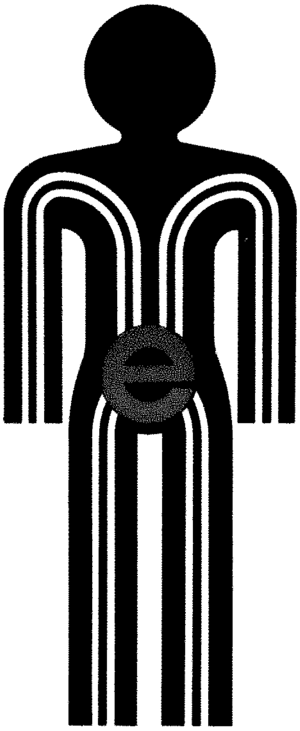

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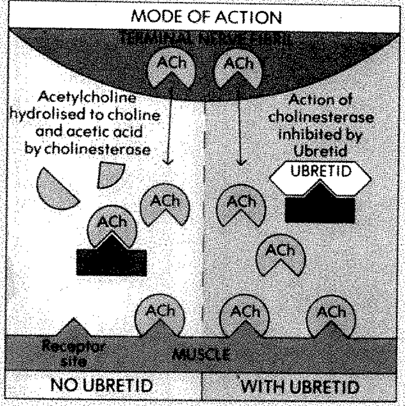
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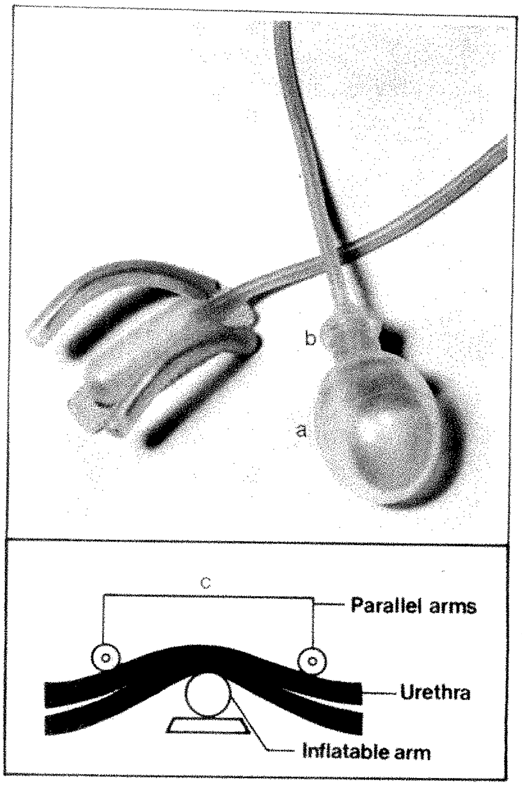

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Renal Mobility in Women Attending a Pyelonephritis Clinic and in Controls

W. N. T. THOMSON, J. A. INNES, J. F. MUNRO, A. M. GEDDES, R. J. PRESCOTT and J. McC. MURDOCH

Eastern General Hospital and City Hospital, Edinburgh; University of Edinburgh; and East Birmingham Hospital, Birmingham

Summary—The range of vertical renal mobility was established in a group of 129 healthy female subjects and compared with the range of mobility observed in 236 female patients attending a pyelonephritis clinic.

The mobility was significantly greater on the right side in both groups and both kidneys moved significantly more in the patient group than in the controls. Excessive mobility could not be directly related to bacteriologically confirmed infection, renal pain or IVP abnormality.

Nephroptosis remains an enigma and excessive renal mobility must not be interpreted in isolation.

Abnormal mobility of the kidney may cause symptoms either as a result of stretching of the renal pedicle or of kinking of the ureter. However, considerable mobility may be observed in symptom-free subjects and the relationship between renal mobility and urinary symptoms in general and liability to urinary tract infection in particular, remains uncertain.

We report a study in which the degree of renal mobility in female patients attending a pyelonephritis clinic is compared with that observed in a control group.

Patients and Methods

A consecutive series of female patients referred to a pyelonephritis clinic was examined. Reasons for referral included persistent symptomatic and asymptomatic bacteriuria, urinary symptoms in the absence of bacteriologically confirmed infection and pain in the loins and back. The age, height, weight and parity of each patient were recorded and the incidence of significant bacteriuria and loin pain was noted. Excretion urography was performed without abdominal compression and films were taken in the supine and erect positions. Abnormalities of the upper urinary tract were recorded independently by 2 observers and a further opinion was obtained if their assessments conflicted.

The mobility of the kidney in the vertical plane was obtained from the erect and supine films by measuring the distance of the upper pole of each kidney from a horizontal line projected from the upper border of the second lumbar vertebra. Films from patients in whom the upper renal border could not be identified were excluded as were films in which the measured depth of the second lumbar vertebra varied by more than 0.1 cm in order to eliminate artefact caused by differences in the angle of projection between erect and supine films.

Measurements were obtained from 236 patients including 2 who had previously undergone right and left nephrectomy respectively. Plain abdominal radiographs in the erect and supine positions were obtained from a control group of female patients who gave their informed consent and had no history of urinary symptoms but were attending hospital medical, diabetic and gynaecological out-patient departments.

Table 1

	Controls	*Patients*
Age (years)	32.3	34.8
Parity	1.4+0.2	1.9+0.3
Height (cm)	162.2	161.3
Weight (kg)	60.0	58.8
Ideal weight (%)	99.9	98.2

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Accepted for publication 2 December 1977.

Measurements were made in a similar manner, films being rejected if the upper renal poles were indistinct or if there was variation in the depth of the second lumbar vertebra. Full measurements were made in 129 control subjects.

The control group was broadly comparable in terms of mean age, parity, height, weight and percentage of ideal weight with the patient group (Table 1). The patients were slightly older and had a correspondingly higher parity.

Results

The mean vertical renal mobility among the controls was, on the right side, 3.24 cm (SD 2.32 cm, range 0 to 89 cm) and, on the left side, 2.66 cm (SD 1.66 cm, range 0 to 6.7 cm). Among the patients the mean drop on the right side was 4.65 cm (SD 2.65 cm, range 0 to 11.7 cm) and on the left 3.76 cm (SD 1.99 cm, range 0 to 11.1 cm). To avoid assumption about the distribution of results, the 2 groups were compared by means of the Kolmogorov-Smirov test. This shows a difference in renal mobility between the 2 groups significant at the 0.001 level on both sides.

Mobility was considered to be excessive if it exceeded the mean value for the control group plus 2 standard deviations (7.9 cm on the right side and 6.0 cm on the left). This was present on the right side in 8 controls (6.2%) and on the left in 7 controls (5.4%) (Fig. 1). Among the patients excessive mobility was noted on 34 occasions (14.5%) on the right and on 30 occasions (12.8%) on the left (Fig. 1). The differences between the 2 groups are statistically significant at the 5% level.

Using multiple regression techniques, further analysis of the data obtained from the patients was undertaken in an attempt to correlate excessive mobility with age, height, weight and parity but there was no significant relationship. One hundred and twenty patients had bacteriologically confirmed infection with at least 10^5 organisms/ml on 2 consecutive clean catch mid-stream specimens of urine either at the time of referral or during the period of follow-up. Figure 2 shows that the degree of renal mobility observed in those patients with and without infection was comparable. A history of right-sided loin pain was obtained from 124 patients and of left-sided pain from 95 patients. IVP abnormality was present in 108 (46%) right kidneys compared with only 48 (20.4%) left kidneys. Loin pain or IVP abnormality was present bilaterally in 55 and 38 patients respectively. Figure 2 illustrates that neither of these features could be related to excessive renal mobility. The difference in incidence of loin pain and IVP abnormality between the sides is statistically significant at the 1% level in both cases (McNemar's Test).

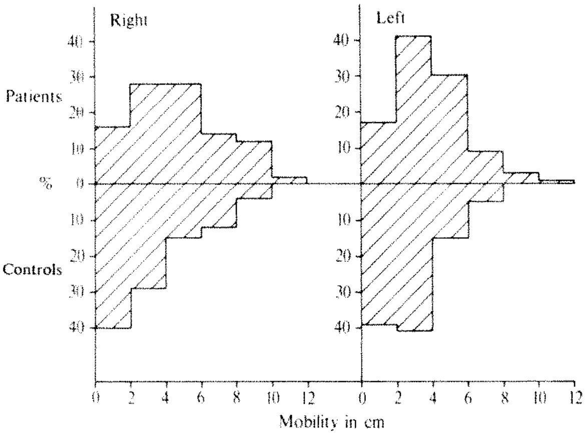

Fig. 1 Renal mobility in patients and controls.

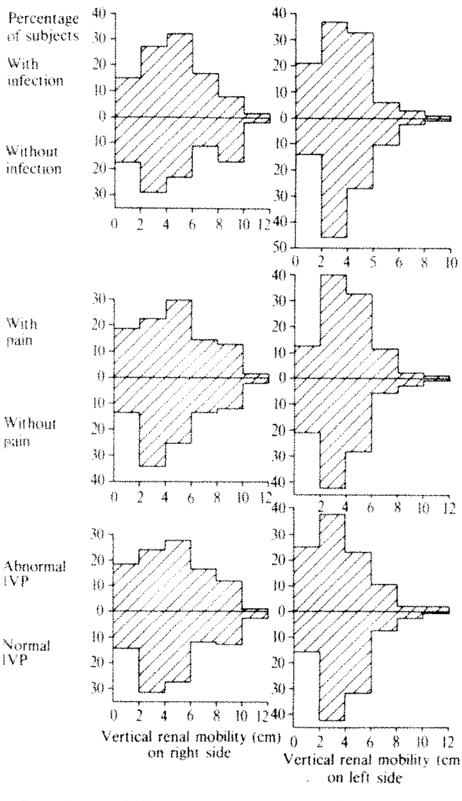

Fig. 2 Renal mobility related to infection, pain and abnormal IVP.

Discussion

Various clinical syndromes have been attributed to abnormal renal mobility (Narath, 1961; Donaldson *et al.*, 1967; De Zeeuw *et al.*, 1977) but few attempts have been made to establish a normal range in healthy individuals. In a study of healthy university students aged 18 to 25 years using plain abdominal radiography Moody and Van Nuys (1940) found that the vertical excursion with posture or respiration in women was between 0.1 cm and 7.5 cm in 96% of right kidneys and in 99% of left kidneys. In a recent report on the association of renal mobility with hypertension De Zeeuw *et al.* (1977) studied 234 patients without obvious genitourinary disorders by excretion urography. They assessed the degree of ptosis by reference to the lower pole of the kidney to exclude the effect of torsion. The mean right renal mobility in female controls was 3.4 cm (SD 2.1 cm) and the mean left renal mobility 3.5 cm (SD 1.8 cm). The figures in male controls were lower, confirming a previous study (Stolze *et al.*, 1958). Nimmon *et al.* (1975) have shown that the mean drop between supine and sitting positions is 2.3 cm in both kidneys but they do not describe the group of patients studied.

This study was confined to adult women. We have shown that the right kidney is significantly more mobile than the left and that there is a considerable range of mobility on both sides in the absence of any history to suggest renal or urinary tract disease. The group of patients referred to the pyelonephritis clinic was comparable in terms of age, height, weight and parity with the control group and although the latter was not subjected to excretion urography we believe that this did not bias the results.

We have demonstrated that there is a highly significant difference in renal mobility between the control and patient groups but have failed to show any significant association between mobility and the presence or absence of bacteriologically confirmed infection, renal pain or IVP abnormality. Thus although mobility appears to contribute to the symptom-complex of "pyelonephritis" its role remains uncertain. Clearly the pathological consequences of excessive renal mobility depend not only on the degree of vertical drop but also on rotational movements, the development of ureteric kinking and the length of the renal pedicle. Indeed we have observed a "postural renal artery stenosis syndrome" in a patient whose renal mobility was not excessive.

In our patients, excretion urography showed that a significant renal abnormality was more than twice as common on the right side. This confirms the observation of others (Speirs *et al.*, 1970) but has never been satisfactorily explained. If the greater mobility of the right kidney predisposed to ureteric obstruction and thus to infection one might expect IVP abnormalities to be commoner on that side.

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Diuresis Renography in Equivocal Urinary Tract Obstruction

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Summary—A trial of the value of diuresis renography in equivocal upper urinary tract obstruction is presented.

Fifty-two patients were examined by standard renography and renography under a diuretic provocation.

The results indicate that the technique is of considerable value in making the vital distinction between dilatation on the excretion urogram due to atonicity and that caused by a genuine obstruction.

A quantitative index of the response to diuresis reflecting the degree of impedance to flow is described—the Diuresis Excretion Index.

Diuresis renography is recommended in the evaluation of the patient with equivocal urinary tract obstruction.

It is well recognised that dilatation of the upper urinary tracts can occur in the absence of obstruction. This is usually because of atonicity of the normal elasto-muscular tissues of the renal pelvis and ureter. Dilatation of the renal pelvis mimicking pelviureteric junction (PUJ) obstruction, residual fullness of the renal pelvis after pyeloplasty, non-refluxing megaureter and ureteric dilatation after reimplantation are 4 situations where the term equivocal urinary tract obstruction may be particularly applicable.

Clinical evaluation in these conditions is often misleading while intravenous urography and ultrasonography provide static, anatomical assessments where a dynamic, functional one is required. Perfusion studies to obtain pressure/flow statistics are well established (Whitaker, 1973, 1976; Whitfield *et al.*, 1976) but are necessarily invasive and not widely practised.

This paper describes a non-invasive method of investigating patients with equivocal upper tract obstruction using radioisotope methods combined with a diuretic provocation technique to clarify the drainage characteristics through the dilated system.

Patients and Materials

Fifty-two patients were examined (Tables 1 and 2). All had suspected unilateral obstruction, 2 in single kidneys. All patients had renography with and without a diuretic stimulus. The renograms were performed using an intravenous injection of 30 μCi of 131-iodine labelled hippuran. The renal handling of this was monitored by a probe scintillation detector

Table 1 Patients Examined by Diuresis Renography

Suspected pelviureteric junction obstruction	26
Pelvic dilatation after pyeloplasty	4
Primary megaureter	6
Ureteric dilatation after reimplantation	4
Miscellaneous	12

Table 2 Miscellaneous Patients Examined by Diuresis Renography

Loin pain/haematuria syndrome
Unexplained loin pain
Mild hydrocalycosis. ?Cause
Retroperitoneal fibrosis
Extrinsic ureteric compression (2)
Radiolucent calculus (undiagnosed)
Ureterocele (2)
Vesico-ureteric reflux with pelvic dilatation
Ureteric dilatation after ureterolithotomy
Upper calyceal dilation. ?Cause

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placed over each renal area. The probes were incorporated into a dental-type chair using surface anatomical landmarks for renal localisation. Additional probes were available for detecting bladder and blood background activity. The detectors were connected via a ratemeter to a chart recorder giving a graph of renal activity with respect to time in the classical manner.

Methods

Each patient had a standard renogram. These were performed with the patient sitting and conscious with no particular preparation other than a check that the subject was in a normal state of physiological hydration and had not had any radiological procedures involving the use of intravenous contrast media in the preceding 48 h. When this study was completed, the patient was asked to empty his bladder and was repositioned. An oral fluid load of 500 ml of water or fruit juice was given followed by an intravenous injection of the diuretic frusemide at dose of 0.5 mg/kg body weight. Four minutes later, the renogram was repeated in the same way. At the end of the test, the patient emptied his bladder, the volume of urine was measured and the investigation concluded.

If the initial renogram showed an obstructive pattern with little or no excretion of tracer after 30 min, the diuretic was given in continuity as the tracing proceeded uninterrupted. Where this was done, the patient subsequently had a further renogram giving the diuretic from the beginning. In all cases the result was the same, indicating that the test can be done in this way if desired. This is convenient because it gives a graphic representation of the effect of the diuretic on the retention of tracer and permits a mathematical estimate of the effect of diuresis to be derived—the Diuresis Excretion Index (DEI *vide infra*).

During diuresis, the urine flow rates in 2 patients with single kidneys were 9 ml/min and 14 ml/min while in patients with 2 kidneys and a suspected unilateral obstruction values ranged between 14 ml/min and 26 ml/min. There were no untoward effects from the test.

Results

It was found that when the initial renograms and the diuretic renograms were taken together, 3 different results were possible.

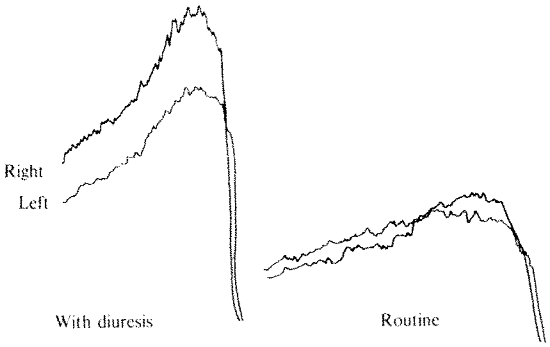

Fig. 1 Response I showing normal initial and diuretic renograms.

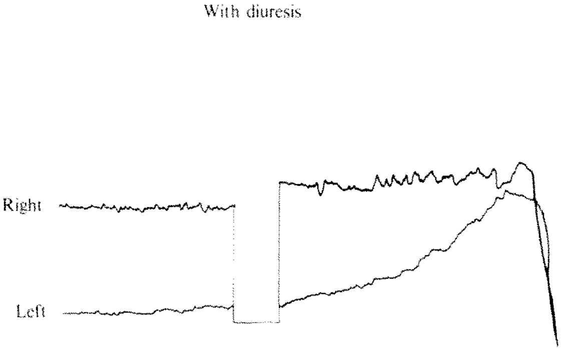

Fig. 2 Response II showing diuretic renogram from patient with initially obstructive pattern, still remaining obstructive under diuresis. Dip in middle = artefact—patient left room to micturate.

I. In the first group, both initial and diuretic renograms were normal with no evidence of any obstruction (Fig. 1). This was true in 5 patients with suspected PUJ obstruction, 1 patient with primary megaureter, 2 patients after ureteric reimplantation and 3 cases in the miscellaneous group (1 loin pain/haematuria syndrome, 1 unexplained loin pain, 1 case mild hydrocalycosis). This finding effectively excluded the presence of obstruction. All patients showing this response remain well with no evidence of deteriorating renal function or further significant symptomatology.

II. In the second group, both initial and diuretic renography showed an obstructive pattern, the increased flow having no appreciable effect on the curve (Fig. 2). This was found in 9 cases of suspected PUJ obstruction, 1 patient after a pyeloplasty, 1 primary megaureter and 1 patient after reimplantation of the ureter. It was also the pattern seen in 4 of the miscellaneous group. Of the 9 cases of suspected PUJ obstruction, the renogram diagnosis was confirmed in every case at operation. The renogram appearances reverted to normal following Anderson-Hynes pyeloplasty. Of the 4 cases in the miscellaneous group, the presence of a genuine obstruction was similarly confirmed at operation in every case—1 patient had retroperitoneal fibrosis, 2 had extrinsic ureteric compression and 1 had an undiagnosed radiolucent calculus. The other 4 cases in which this result was found are undergoing further assessment. All are symptomatic and likely to be candidates for surgical exploration. This result is thus indicative of a genuine obstructive lesion in the upper tract.

III. The third result is that in which an initial obstructive pattern is altered by the diuresis. This alteration may be of 2 kinds:

(*a*) A sudden brisk and rapid elimination of the retained activity in response to the diuretic (Fig. 3a). This was found in 10 cases of suspected PUJ obstruction, 2 postpyeloplasty cases, 3 primary megaureter and 1 case after reimplantation of the ureter. It was also found in 5 of the miscellaneous cases (2 ureterocele, 1 vesico-ureteric reflux with pelvic dilatation, 1 dilatation after ureterolithotomy and 1 upper pole calyceal dilatation of uncertain aetiology).

This result is the picture found in the "mixing chamber" situation where an atonic dilatation is present without obstruction causing sluggish flow and retention of tracer in the field of the detector. The diuresis clearly reveals the true situation allowing unimpeded excretion through the dilated system.

It is significant that in all the renograms showing this pattern, the slope of phase 2 was similar to that of the contralateral normal kidney, indicating preservation of underlying renal function—further evidence against the presence of a significant obstructive process.

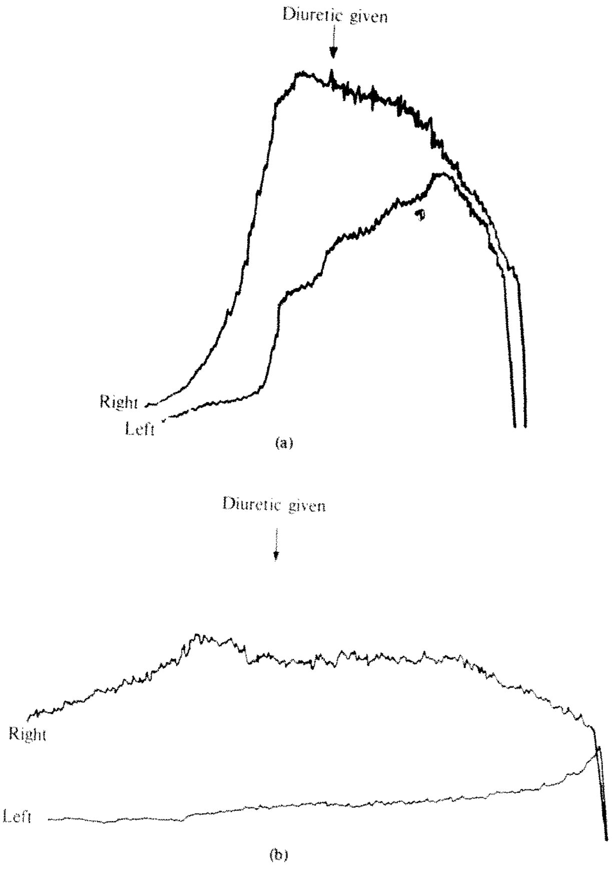

Fig. 3 Response IIIb. Initially obstructive pattern showing only partial improvement under diuresis.

Furthermore, 2 patients investigated in the early part of this study underwent pyeloplasty operations. In both cases the renal pelvis appeared macroscopically normal, and when examined by light and electron microscopy showed none of the classical changes associated with obstruction, but were in all respects normal also.

Table 3 Results of Diuresis Renography

Urinary tract dilatation	*Response*			
	I *(normal)*	II *(obstruction)*	III(*a*) *(atonic)*	III(*b*) *(? subtotal obs.)*
?PUJ obstruction	5	9	10	2
Postpyeloplasty		1	2	1
Primary megaureter	1	1	3	1
Postreimplantation	2	1	1	—
Miscellaneous	3	4	5	—

(*b*) The second response to diuresis is an improvement in excretion which is by no means as impressive as in the preceding group and where phase 3 remains flatter than normal (Fig. 3b). This was found in 2 cases of suspected PUJ obstruction, 1 postpyeloplasty case and 1 primary megaureter.

This finding is indicative of the presence of a degree of subtotal impedance that is partially overcome by the increased flow, but not completely.

These results are summarised in Table 3.

The Diuresis Excretion Index

When the diuretic provocation is given in continuity during an obstructive renogram (where little or no elimination has occurred after 30 min), it is possible to quantitate the consequent improvement in the rate of excretion. This is done by measuring the change in slope of the third phase of the renogram at the time the frusemide takes effect. A simple index of this change in slope is the difference between the fall in count rate during the first 3 min after the peak in the renogram and the fall—if any—in the preceding 3 min (Fig. 4). This difference is expressed as a percentage to give the Diuresis Excretion Index (DEI). If no peak is seen, the reference point is taken as being at 3 min after the injection of frusemide at which time the diuretic begins to take effect on the renogram curve.

In the obstructive pattern where there is no response to the diuretic, the DEI is zero. The mixing chamber effect, where excretion commences promptly, usually gives values in excess of 30%. Values between, may reflect some degree of subtotal obstruction.

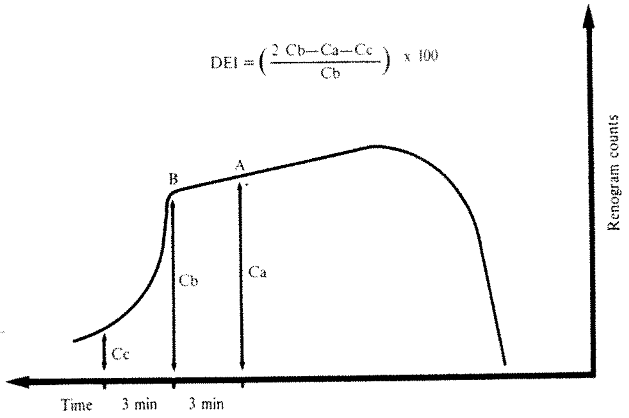

Fig. 4 The Diuresis Excretion Index.

Discussion

Isotope renography gives more information than urography on function and emptying rates from individual kidneys. However, investigators who have used it in the past in equivocal urinary tract obstruction differ in their views as to its true value. Some have reported it as useful (Santiago, 1969; Hisazumi *et al.*, 1972; Karlberg, 1976) while others have emphasised possible shortcomings which they feel make it impracticable (Davies *et al.*, 1969; Roberts *et al.*, 1972; Whitaker, 1973). The main objections appear to be that quantitation of physiological measurements from the probe renogram curve is unreliable, and that the sluggish flow through a distended tract gives a curve indistinguishable from that found in genuine obstruction.

The clinician requires to know whether or not the apparently dilated upper urinary tract is truly obstructed and the present trial has attempted to answer that question by combining standard renography with renography under conditions of increased flow. In the absence of obstruction, the increased capacity should be of little importance in relation to urine flow and excretion should proceed unimpeded. Conversely, a genuine obstruction might be expected to cause an impedance at low or high flow rates.

Our results indicate that such a technique can be of value in making this distinction. Since the initial study, a further 80 patients between the ages of 3 months and 60 years have been examined. In every case where initial and diuretic renograms have been obstructive, a true obstruction has been found at operation. Post-operative examinations have shown marked improvement. Of 15 post-operative pyeloplasty patients, 12 have shown an apparently obstructive pattern on renography for the same reason that the intravenous urogram rarely returns to normal—residual atonicity. All of these curves were converted to normal by diuresis reflecting the true situation.

Work is now in progress to correlate the diuretic renogram with diuresis pyelography, perfusion studies and morphological abnormalities as seen on light and electron microscopy. Preliminary work in the latter trial indicates exact correlation between the Diuresis Excretion Index and the degree of morphological abnormality as judged on a double blind basis.

Quantitative assessment of renal function before and after operation in these cases is possible by deconvolution of the probe renogram and by gamma camera evaluation of intra-renal dynamics.

These isotope studies are non-invasive, rapid, non-toxic and carry a low radiation dose to the patient. Their combination with diuretic techniques allows an assessment of the function and the drainage capability. They are recommended in all states of equivocal obstruction before proceeding to more invasive procedures.

Acknowledgements

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Cytological Changes due to Urinary Calculi

A Consideration of the Relationship between Calculi and the Development of Urothelial Carcinoma

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Summary—Urinary calculi can induce urothelial cellular abnormalities comparable with those of malignancy; this was found in 11 out of 62 lithiasis cases.

Severe cellular changes, comparable with those of carcinoma *in situ*, may be seen in the epithelium adjacent to a calculus. Squamous metaplasia was frequently observed in cases with staghorn stones in the renal pelvis. The abrasive effect of the calculus may result in many multinucleated cells in the sediment.

When the calculi are removed the cytological atypia and the observed multinucleation disappeared, and none of these 62 patients developed urothelial carcinoma.

A possible relationship was found between a long-term clinical history of lithiasis and the development of cancer of the upper urinary tract in a study of 92 cases of carcinoma of the ureter and renal pelvis.

In reports concerning the accuracy of the cytological diagnosis of cancer of the urinary tract it has been repeatedly recorded that urine from patients with urinary calculi may contain cells interpreted as malignant, whereas the presence of urothelial carcinoma could not be established (Deden, 1954; Foot *et al.*, 1958; Seybolt, 1960; Umiker *et al.*, 1962; Taylor *et al.*, 1963; Wiggishoff and McDonald, 1969; Esposti *et al.*, 1970; Esposti and Zajicek, 1972; Tyrkko, 1972).

In order to study changes induced by calculi we collected 62 lithiasis cases. The purpose of this paper is to present and discuss the cytological abnormalities during and after the presence of the calculi and to study the relationship between calculi and the development of urothelial carcinoma in a group of 92 patients with proven cancer of the renal pelvis and ureter.

Cytological Abnormalities and Calculous Disease

Material and Methods

From the files of the Cytology Laboratory of the Department of Pathology smears from 62 patients with lithiasis of the urinary tract were extracted. We used fresh, spontaneously voided specimens of urine with the exception of 1 case of catheterised urine. Smears from the sediments obtained by centrifugation were stained with the Papanicolaou method after wet fixation with 95% ethanol, or spray fixative, and by May Gruenwald Giemsa (MGG) method after air-drying (Beyer-Boon, 1977c). We used the cytological criteria of malignancy in Papanicolaou-stained cells as described by Esposti *et al.* (1970) and in MGG-stained cells as published by us (Beyer-Boon *et al.*, 1977a). The application of the MGG method in urinary cytology proved to be of great value, especially in blood specimens because in this stain the erythrocytes do not interfere with the microscopic evaluation of the epithelial cells. Moreover, the yield of epithelial cells is maximal because cell loss does not occur in air-dried material during the staining procedure.

In addition, most specimens were examined by phase contrast microscopy (de Voogt *et al.*, 1975). The cytological diagnoses used by us are: positive for malignancy, suspicious, atypia and negative for malignancy. For the histological classification of urothelial tumours we used the system of Bergkvist *et al.* (1965), and the flat intra-epithelial *in situ* carcinomas were graded as recommended by Barlebo *et al.* (1972).

The urinary calculi from 45 patients were chemically analysed. In all the lithiasis patients

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Table 1 Clinical and Cytological Data on 18 Patients (all males) with Urinary Calculi, and Chemical Data on the 10 Analysed Calculi

Patient	*Location of calculi*	*Components of calculi**			*Cytological diagnosis calculi present*	*Inflammatory background*	*Multinucleated "malignant" urothelial cells (%)*	*Multinucleated "benign" urothelial cells (%)*
		1	*2*	*3*				
1	Pelvis and ureter	5	41	49	Suspicious	+	6	12
2	Pelvis	1	18	74	Positive	+ + +	8	7
3	Ureter	7	36	62	Positive	–	15	20
4	Bladder	–	21	82	Positive	–	20	11
5	Bladder	35	–	56	Positive	–	34	10
6	Pelvis	–	–	–	Positive	+	8	6
7	Pelvis and bladder	6	32	68	Positive	+	8	5
8	Pelvis	1	8	88	Positive	+ +	4	7
9	Ureter	4	9	82	Positive	+ + +	10	15
10	Ureter	–	–	–	Positive	+	10	8
11	Ureter	–	–	–	Positive	–	5	8
12	Pelvis	2	14	83	Atypia	+	–	8
13	Ureter	–	–	–	Atypia	–	–	6
14	Pelvis	56	32	8	Atypia	+ +	–	15
15	Unknown	–	–	–	Atypia	+	–	15
16	Voided	–	–	–	Atypia	–	–	10
17	Voided	–	–	–	Atypia	+ +	–	6
18	Voided	–	–	–	Atypia	+ +	–	12

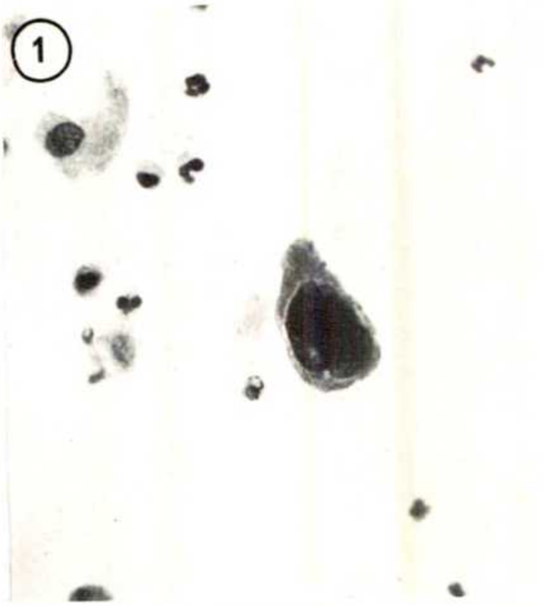
* 1. Struvite (Mg NH_4 PO_4 H_2O). 2. Apatite (Ca 10 (PO_4) (OH)2). 3. Wheddelite (Ca $C_2O_4H_2O$).

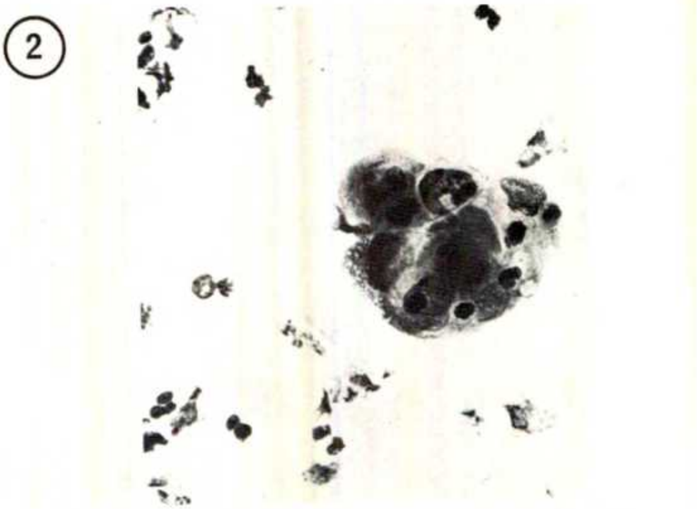
with a positive cytological report, extensive clinical examination was combined with multiple bladder biopsies to ensure that a urothelial malignancy was not overlooked. All patients with abnormal cells in their urinary sediments had a follow-up ranging from 1 to over 5 years. The cytological and histological patterns induced by lithiasis were compared with those of carcinoma *in situ*.

Results

The cytological diagnoses were reported as positive for cancer in 10 cases, suspicious in 1 case, atypical in 7 cases (Table 1) and negative in 44 cases. The cytological picture in 8 positive cases and 1 suspicious case was thought to be compatible with grade 2 carcinomas (Figs. 1 and 2). In them the nuclear area in the Papanicolaou method ranged from 32 to 96 μ^2; most nuclei were between 60 and 70 μ^2. In the 2 other positive cases the abnormal cells were compatible with grade 3 neoplasms (Figs. 3 and 4) and had nuclear areas ranging from 50 to 152 μ^2, with a predominance of nuclei between 80 and 90 μ^2. Using the MGG method these nuclear areas were nearly doubled. The cytological picture became normal after the calculi were removed and remained normal for periods of 1 to 5 years in all of the 9 patients from whom we received a urine specimen after operative or spontaneous elimination of the stone. In 1 of these the cytological pattern remained abnormal between pyelolithomy and litholapaxy, returning to normal after litholapaxy. One of the remaining 2 patients died before the calculus was removed: at autopsy a renal calculus was found, but no tumour growth. In the other the stones were not removed completely at operation and after 4 years there are no gross signs of tumour growth.

In addition to nuclear abnormalities, we noted the occurrence of multinucleated urothelial cells in the cytologically abnormal, as well as in the cytologically negative, sediments and also in both the cytologically "benign" (Fig. 5) and "malignant" cells (Figs. 1, 3 and 6) (Table 1). The classification of the cells as benign or malignant was made exclusively on the texture, and not on the size, of the nuclei. Some "benign" multinucleated urothelial cells contained very large nuclei which, in the Papanicolaou-stained specimen, had areas of up to 180 μ^2. In the sediment of patient 5 (Table 1), for example, 14% of the epithelial cells were binucleated, 6% were trinucleated and 14% contained more than 3 nuclei. We also observed that the proportion of





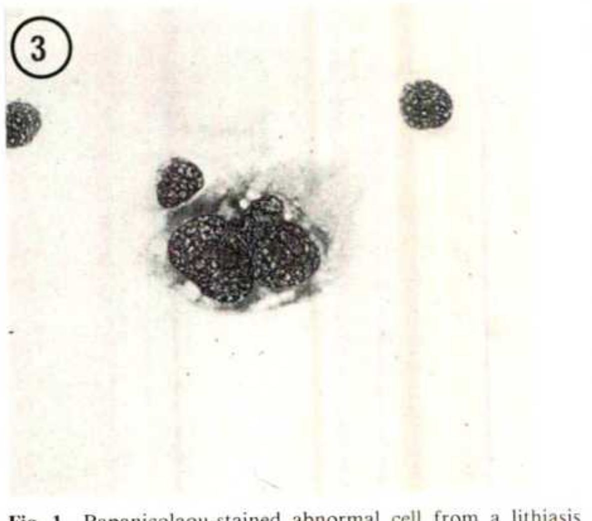


Fig. 1 Papanicolaou-stained abnormal cell from a lithiasis case with a positive cytological report. Note multinucleation, hyperchromasia and abnormal chromatin structure (×500).

Fig. 2 Group of MGG-stained cells in a lithiasis case with a positive cytological report. Chromatin is abnormal and the nuclei contain macronucleoli (×400).

Fig. 3 MGG-stained binucleated cell from a lithiasis case with a positive cytological report. Chromatin is abnormal and the nuclei contain macronucleoli (×400).

multinucleated cells increased during an attack of renal colic, and that, in all patients whose post-operative urine was examined, the multinucleation disappeared after the calculi had been removed. To rule out other possible causes of multinucleation, such as catheterisation, we examined spontaneously voided urine in all but 1 case. It was also noted that many patients, especially those who harboured stones in the renal pelvis for a long time, had many squamous cells in the urine, suggestive of squamous metaplasia of the urothelium.

The locations of the calculi of the cytologically negative cases are shown in Table 2. In the cytologically abnormal cases the calculi were found in the sites shown in Table 1. From this data it is not possible to conclude from contingency tables whether or not there is a

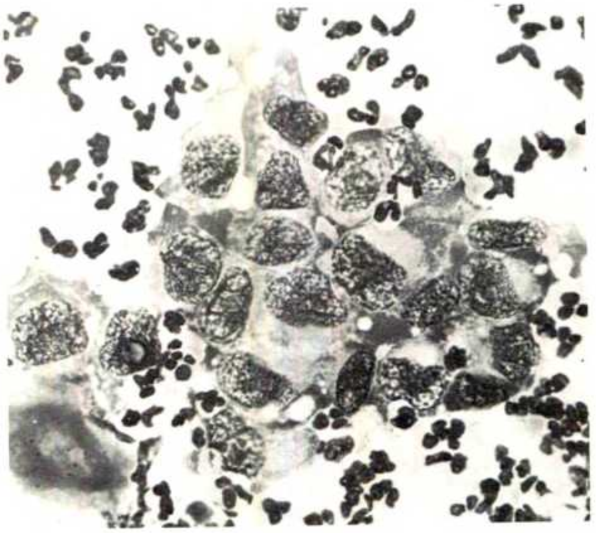


Fig. 4 MGG-stained cells from a lithiasis case with positive cytology. Note the irregular shape of the nuclei and the abnormal chromatin structure (×500).

correlation between the location of the calculus and the cytology report.

The stones from 10 of the 18 patients with abnormal cytological findings (listed in Table 1), and from 35 of the 44 patients with negative cytological findings (Table 2) were analysed chemically but there was no significant relationship between their composition, their location or the cellular abnormalities they induced.

In all the lithiasis cases with a suspicious or positive cytological report, extensive clinical examination combined with multiple bladder biopsies were performed. To date no patient has developed a urothelial carcinoma. This is not surprising in those cases where the calculus was removed, since the cell atypia associated with calculi disappeared when they were no longer present, but is, perhaps, unexpected in the patient whose calculus could not be removed and in whom the cytology remained abnormal.

In 9 of our 11 "false positive" lithiasis cases the cytological picture was less polymorphic than in the majority of the carcinoma *in situ* cases previously reported by us (de Voogt and Beyer-Boon, 1976). In all lithiasis cases there were fewer abnormal cells than in the carcinoma *in situ* cases, but the numbers were comparable with those seen in cases of highly differentiated, early infiltrative papillary urothelial cancer (Bergkvist grade 2 tumours). In the lithiasis cases (Fig. 4) an inflammatory background was also frequently present. The percentage of the multinucleated morphologically malignant cells in the false positive lithiasis cases varied from 4 to 34% with a mean of 12.3%. In the carcinoma *in situ* cases the percentage of morphologically *malignant* multinucleated cells was never higher than 10 with a mean of 6, and in contrast with the lithiasis cases (Fig. 3) no more than 2 nuclei per cell were found. In the lithiasis cases in addition morphologically *benign* multinucleated urothelial cells were frequently found (Table 1), in contrast with the carcinoma *in situ* cases.

Table 2 Forty-four Patients with Calculi and Negative Cytology

Sex		*Location of calculus*	
Male	39	Pelvis	13
Female	5	Ureter	8
		Bladder	15
		Unknown	7

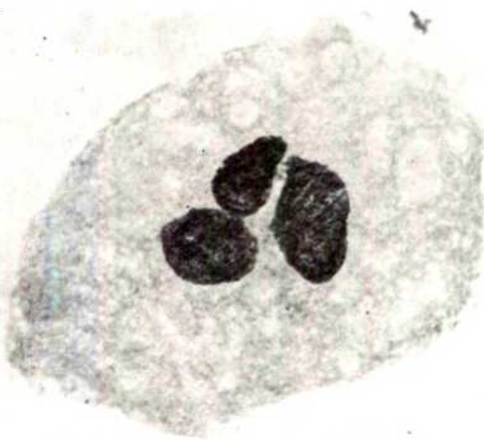


Fig. 5 MGG-stained multinucleated cell from a case with negative cytology. The large nuclei are regular and display no chromatin abnormalities (×500).

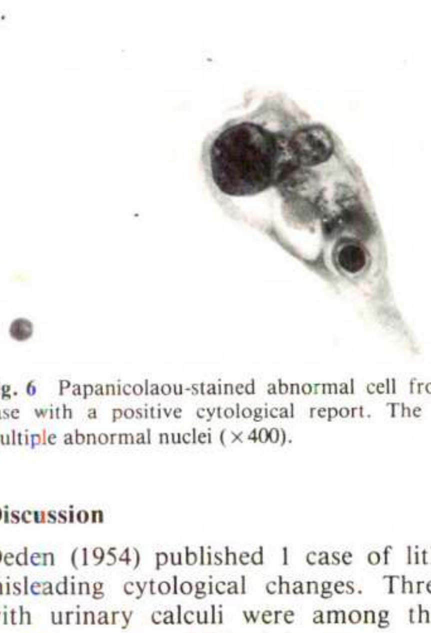


Fig. 6 Papanicolaou-stained abnormal cell from a lithiasis case with a positive cytological report. The cell contains multiple abnormal nuclei (×400).

Discussion

Deden (1954) published 1 case of lithiasis with misleading cytological changes. Three patients with urinary calculi were among the 10 false positive cases published by Foot *et al.* (1958). Esposti *et al.* (1970) and Esposti and Zajicek (1972) described 8 cases with cells suspicious for malignancy in their series of 207 patients without urothelial carcinomas. One patient had cystitis, 1 had prostatitis and 2 had urinary calculi. Seybolt (1960) mentioned calculi as a special source of false positive diagnoses in urinary cytology and Taylor *et al.* (1963), Umiker *et al.* (1962), Wiggishoff and McDonald (1969) and Tyrkko (1972) encountered difficulties of interpretation in patients with urinary calculi. However, in the 5 latter publications no numerical analyses of the false positive and suspicious diagnoses were given. These authors mentioned inflammation of urothelium and prostate gland, prostatic hypertrophy, ionising radiation, squamous metaplasia and hormonal treatment as other causes of erroneous diagnoses, though it is our experience that in these cases very atypical cells may be detected (Beyer-Boon *et al.*, 1977).

The presence of "comet" or "decoy" cells may also lead to an erroneous diagnosis of cancer (Crabbe, 1971). These are described as cells with round or oval hyperchromatic nuclei, a coarse chromatin pattern and a small tag of cytoplasm or no cytoplasm at all. The abnormal epithelial cells seen in our lithiasis cases had additional nuclear features, such as irregular nuclear form and multiple nucleoli, and cannot, therefore, be regarded as comet cells.

The nuclear size of the "malignant" cells in 8 positive cases and 1 suspicious case were in the same range as encountered in typical examples of grade 2 carcinoma cases, and in the 2 remaining positive cases were as in grade 3 carcinomas (Kern, 1975).

The percentage of multinucleated cells in the lithiasis cases was higher than is usually encountered in smears of patients with transitional cell carcinoma. Morphologically benign multinucleated cells are always encountered in urine collected by abrasive techniques, such as catheterisation, and in the voided urine of elderly men with hypertrophy of the prostate. In the latter, the nuclear area is seldom over 80 μ^2 in the Papanicolaou method and over 150 μ^2 in the MGG method. When distinguishing between the changes due to lithiasis and carcinoma *in situ*, the number of abnormal cells, the predominance of uniform abnormal cells, the high percentage of multinucleated cells (both morphologically benign as well as malignant) and the occurrence of more than 2 nuclei in a single epithelial cell will prove to be the major cytological criteria, although a combination of lithiasis and carcinoma *in situ* can never be excluded on morphological grounds alone.

Many cases are published in which the cytology was positive for a long period of time before histological proof of cancer was established (Koss *et al.*, 1969); however, in our carcinoma *in situ* cases (without lithiasis) the histological confirmation of the cytological diagnosis took, at the most, 7 months (de Voogt and Beyer-Boon, 1976). Moreover, in all our carcinoma *in situ* cases the lesion proved to be multifocal and "recurrent" (de Voogt and Beyer-Boon, 1976). In this context the lithiasis patient No. 10 is of particular interest, as it was suspected there was a malignant neoplasm of the ureter, whereas the urogram was abnormal and the cytology had been reported positive. The ureter was explored and appeared to contain a calculus. The transitional epithelium where the calculus had been located showed considerable nuclear polymorphism and hyperchromasia, loss of polarity of the epithelial cells and mitotic figures high in the epithelium (Fig. 7), changes comparable with urothelial carcinoma *in situ* (Koss, 1975). In this case no "recurrence" was detected in the follow-up period of 69 months, in contrast to the frequently encountered "recurrent" cytological and histological signs of cell abnormalities in carcinoma *in situ* cases (Utz *et al.*, 1970).

Reports on a possible aetiological relationship between lithiasis and urothelial carcinoma are contradictory. Cases are described such as that of James Ewing who had bladder calculi for a long time and eventually died of disseminated bladder cancer (Koss, 1975). Statistical analyses, as published by Wynder *et al.* (1963) gave no more than

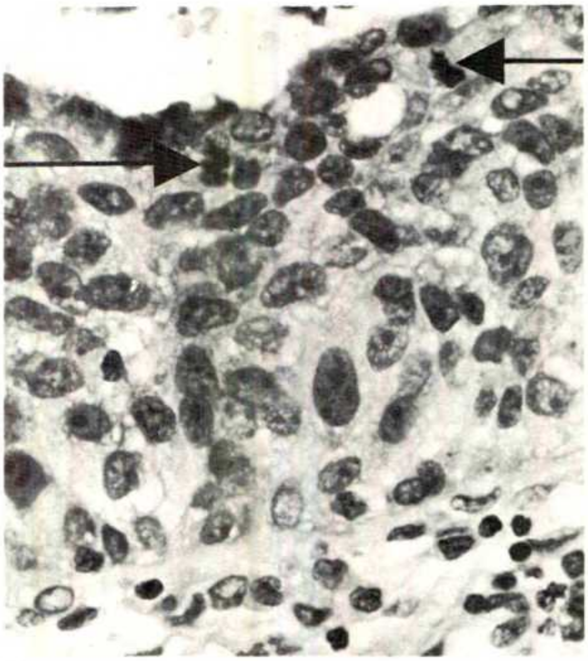


Fig. 7 Tissue section (H & E stain) of ureter, lithiasis patient No. 10. The cell polarity is lost, the irregularly shaped nuclei contain large nucleoli and mitotic figures are found high up in the epithelium (arrows) (×500).

Table 3 Occurrence of Previous or Concomitant Urinary Calculi in Pelvis and Ureter in 14 of 92 Patients with Renal Pelvic and Ureteric Carcinomas

Patient	*Age*	*Previous lithiasis*	*Location of tumour*	*Side*	*Location of calculus*	*Histology*
1	67	–	RPC	L + R	R Pelvis	TCC
2	50	+, L 2 years	RPC	R	R Pelvis staghorn stone	SCC
3	53	+, L 2 years	RPC	R	R Pelvis staghorn stone	Anaplastic carcinoma
4	62	+, L 2 years	RPC	R	R Pelvis staghorn stone	TCC
5	68	–	RPC	R	R Pelvis	TCC
6	58	–	RPC and UC	R	R Pelvis and Ureter	CIS
7	71	+9 years	RPC	L	Unknown	SCC
8	42	+26 years	RPC	R	Unknown	TCC
9	66	+9 years	RPC	L + R	Unknown	TCC
10	56	+10 years	RPC	R	Unknown	TCC
11	67	+30 years	RPC	R	Unknown	TCC
12	74	+9 years	RPC and UC bladder ca	R	R Ureter	TCC
13	46	+21 years	RPC	R	Unknown	SCC
14	49	+8 years	UC	L	L Ureter, L Pelvis	TCC

TCC = Transitional Cell Carcinoma.
UC = Ureteric Carcinoma.
SCC = Squamous Cell Carcinoma.
RPC = Renal Pelvic Carcinoma.
CIS = Carcinoma *in situ*.

suggestive evidence of a positive association of bladder stones and cancer which could not be confirmed by Dunham *et al.* (1968). The absence of a convincing association so far as the bladder is concerned (Seybolt, 1960) may be explained by the fact that only very large stones are likely to influence the extensive surface of the bladder epithelium. In contrast to this, it seemed reasonable to suspect that even the smallest calculus might have an effect on the ureteric and pelvic mucosa and accordingly we turned out attention to cases of renal pelvic and ureteric cancer and studied 92 such cases, taken from the files of 6 major hospitals in the Netherlands (Cuypers, 1975). The histological material was reviewed. Fourteen of the 92 patients had either previous or concomitant lithiasis (Table 3), so that it appears that lithiasis is more common than might be expected in patients with renal pelvic and ureteric cancer (confidence interval P = 99% 5 to 22 per 92). The precise number of people with lithiasis histories in the Netherlands is not known, but it is thought to be considerably less than 5 to 22 per 92 (3 to 5 per 1000 in a clinic of mentally retarded patients and 5 to 7 per 1000 in the practices of 3 general practitioners in Leyden involving patients the same age as our cancer patients).

When localisation of the calculus was known, it was found to be on the cancer affected side of the system (Table 3, patients 1, 2, 3, 4, 5, 6, 12 and 14). In 3 cases (Table 3, patients 2, 3 and 4) the presence of the calculus had not been established for more than 2 years before the diagnosis of cancer was made, so we could not prove which was first, the stone or the tumour. If these cases are excluded it will be seen that 11 are left in which we could establish with certainty that the lithiasis preceded the tumour, the time lapse between the onset of symptoms due to the calculus and the diagnosis of tumour ranging from 4 to 30 years. Martin and Mertz (1917) observed that the average duration of symptoms of lithiasis of 14 of 22 patients with renal pelvic carcinoma was 19 years.

The number of cases with a combination of squamous cell carcinoma and stones was relatively high. The histological diagnosis of squamous carcinoma in the whole group of 92 cases was made in 9 cases (9.9%) whereas in the 14 patients with stones 3 had a carcinoma of this type (21.5%). Riches (1959) found also relatively few stones in the presence of transitional cell carcinoma whereas a frequent combination of squamous cell carcinoma with stones was found by Utz and McDonald (1957) (13 of the 23 cases of squamous cell carcinoma, reported by these authors, had renal pelvic stones).

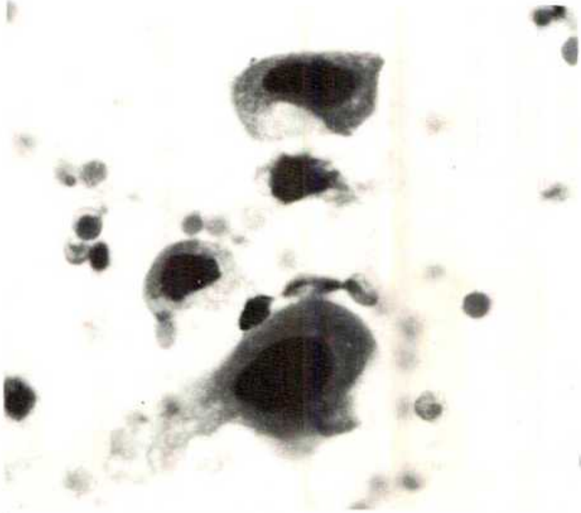


Fig. 8 Papanicolaou-stained cells from Dr Spriggs' case. The nuclei are hyperchromatic and squamoid differentiation of the cells is noted (×400).

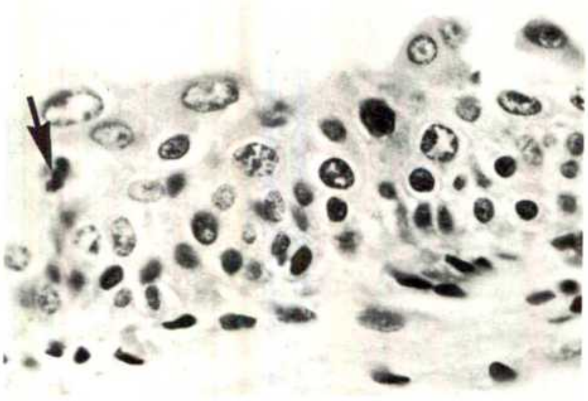


Fig. 9 Tissue section (H & E stain) of the renal pelvic mucosa, Dr Spriggs' case. Atypical squamoid metaplasia. Note mitotic figure (arrow) (×312.5).

It seems therefore that there is a relationship between lithiasis and cancer of the upper urogenital tract. Moreover, from examination of the urinary sediments of our lithiasis patients it can be seen that calculi may provoke cancerous-like changes in individual cells. In addition to these, mitotic figures may be found extending high in the epithelium. These changes in the tissue sections were seen in our study as well as that of Dr A. Spriggs*, who has kindly permitted us to publish Figs. 8, 9 and 10. In this context it is interesting to note that cells exfoliated from bladder cancers, as well as the epithelial cells in the urine sediments of kidney stone patients, have a high labelling index of tritiated cystine, while all the patients without such diseases had low indices (Webber, 1969). Evidently, in stone patients proliferation of the epithelium may occur as rapidly as in cancer cases.

The follow-up period of our 11 patients with suspicious and positive cytology and lithiasis (Table 1) is too short to draw any conclusions concerning a possible relationship between urothelial cancer and stone formation, because in the majority of them the calculus was removed within a short time of the onset of symptoms with a consequent disappearance of the stone-induced cell changes in the urine. It is feasible that the calculus-provoked changes, which are reflected in the nuclear morphology and rate of proliferation, are reversible up to a certain point when, if the stimulus is not removed, the development of carcinoma becomes inevitable. It may be possible that the "point of no return" was not yet reached in our cases in which the cell changes proved to be reversible. The time interval between the onset of lithiasis complaints and the diagnosis of pelvic neoplasm can be up to 30 years (Table 3), and thus the downhill course is not necessarily so fast as seen in our "classical" carcinoma *in situ* cases without lithiasis (de Voogt and Beyer-Boon, 1976).

It is known that there is a close association between squamous metaplasia of the urothelium and lithiasis (Utz and McDonald, 1957). In countries with a high incidence of schistosomiasis, for instance, both squamous metaplasia and bladder stones are frequently encountered (Mustacchi and Shimkin, 1958; Wynder *et al.*, 1963). It is possible that the stone either precedes and induces, or is a result of the metaplastic change of the epithelium (Utz and McDonald, 1957). In 2 of 3 cases of squamous carcinoma of the pelvis, we may assume that the stone preceded the metaplastic change because the stones were attributable to hypercalcaemia (Table 3, cases 7 and 13). In the urine of 1 of the male lithiasis patients (Table 3, case 2) with a staghorn stone in the pelvis we found many squamous epithelial cells (Fig. 11). The tissue sections of the

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* This case was presented at the Symposium on Urothelial Neoplasia, 31st Scientific Meeting of the British Division of the International Academy of Pathology, London, November 1975.

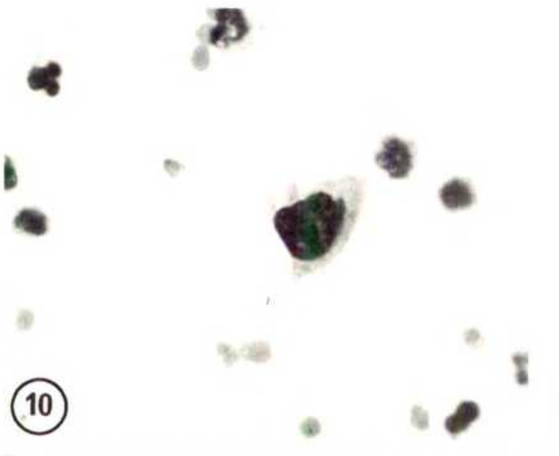

Fig. 10 Papanicolaou-stained cell with abnormally shaped nucleus and large nucleolus, Dr Spriggs' case (×400).

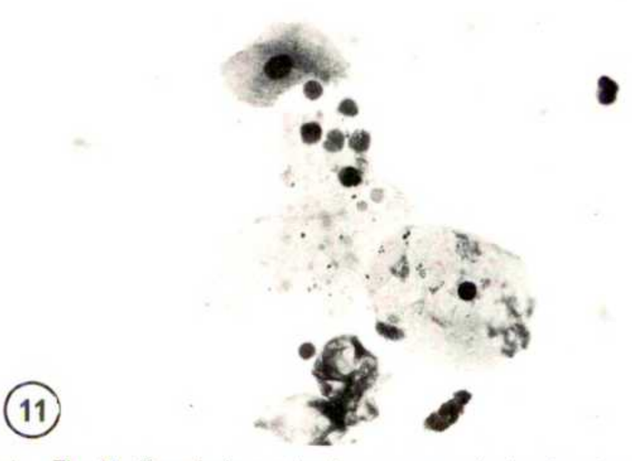

Fig. 11 Papanicolaou-stained squamous cells in the urine from a male patient with a staghorn stone in the renal pelvis (×125).

operation specimen displayed benign squamous metaplasia (Fig. 12). In the case of a "false positive" cytological diagnosis of cancer in the presence of a renal calculus (Dr Spriggs' case), there was a definite squamous differentiation of the abnormal cells in the sediments and the tissue sections (Figs. 8, 9 and 10).

It is conceivable that the atypia associated with lithiasis may prove to have clinical importance comparable with the drug-induced atypia which was thought to "mimic" cancer (Forni *et al.*, 1964). Recent reports (Wall and Clausen, 1975; Beyer-Boon, 1977b) have established that such patients may develop lethal infiltrative bladder cancer. Therefore those patients who have stones and shed abnormal cells must be closely followed because of the possible development of clinical cancer (Scholl, 1933).

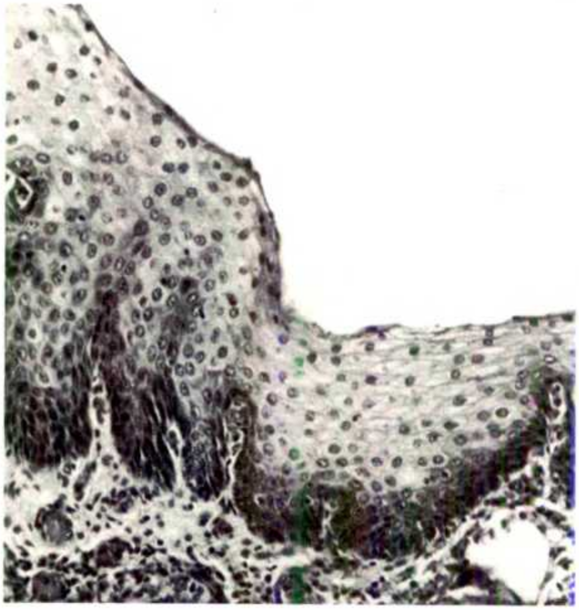

Fig. 12 Tissue section (H & E stain) from the pelvic mucosa with squamous metaplasia. Same patient as in Fig. 11 (×125).

Acknowledgements

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Exstrophy of the Bladder: Treatment by Trigonosigmoidostomy—Long-term Results

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Summary—Twenty-five patients with bladder exstrophy were treated by implanting the vesical trigone into the sigmoid colon. Twenty-three have been followed for 3 to 19 years, with an average of 10 years. Taking into account the clinical status, renal function, the intravenous urogram, continence and social life, 18 patients were considered to have had an excellent result. There were 2 failures; 1 post-operative death occurred due to ruptured oesophageal varices and 1 patient developed bilateral hydronephrosis which necessitated cutaneous urinary diversion. In 4 cases the results, while satisfactory, were only fair in that 2 developed stones and 2 showed symptomatic electrolyte disturbances requiring treatment. Trigonosigmoidostomy preserves intact the ureterovesical junction which prevents colo-ureteric reflux and this probably accounts for the generally excellent long-term results. We believe the operation is preferable to ureterosigmoidostomy in the management of bladder exstrophy.

Exstrophy of the bladder remains one of the ultimate challenges in paediatric urology. Although functional reconstruction seems the ideal solution, no operation can produce a normal bladder. The aim of the surgeon should be to have a continent child with normal social life, preserved renal function with normal upper tract, an acceptable physical appearance and ability to function sexually (Marshall and Muecke, 1970).

Various methods have been used to treat the child with bladder exstrophy, including primary functional closure of the bladder (Fisher and Retik, 1969; Ezell and Carlsson, 1970; Marshall and Muecke, 1970; Cendron, 1971; Jeffs *et al.*, 1972; Megalli and Lattimer, 1973; Williams and Keeton, 1973), ureteroilealcolostomy (Houtappel, 1963), primary ureterosigmoidostomy (Spence, 1966; King and Wendel, 1972; Bennett, 1973; Megalli and Lattimer, 1973), rectal bladder with adjacent colon pull through (Mauclaire, 1895; Heitz-Boyer and Hovelaque, 1912; Lowsley and Johnson, 1955; Duhamel, 1971; Nedelec *et al.*, 1975), vesicoileosigmoidostomy (Hays *et al.*, 1969; Singer and Pompino, 1966), bladder enlargement by intestinoplasty (Cukier and Ott, 1971; Martinez-Pineiro, 1976) and non-refluxing colon conduits (Hendren, 1976).

An alternative approach in patients with bladder exstrophy consists of implanting the isolated trigone in the sigmoid colon. The method was first described by Maydl (1894) and it was widely used in the beginning of this century; Moorhead and Moorhead (1916) reviewed 152 cases. Several slight modifications of Maydl's procedure were reported (Peters, 1901; Fowler, 1898; Moynihan, 1906; Boyce and Vest, 1952; Gregoir, 1968). Experimental studies on urinary diversion through the use of vesico-rectal anastomosis demonstrated a satisfactory preservation of renal function (Boyce, 1951).

The purpose of this report is to present the results of treatment of exstrophy of the bladder by trigonosigmoidostomy in 25 patients.

Patients

Twenty-five patients with classic bladder exstrophy have been treated by trigonosigmoidostomy. The series included only 2 females. The ages ranged from 2 to 30 years (average 6 years). The follow-up period was from 3 to 19 years (average follow-up period 10 years).

This operation was the primary treatment in 23 cases; in 2 cases it was performed after failure of an attempt at bladder reconstruction. The indications for operation were based on 3 factors:

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1. a normal IVP;
2. a normal competent anal sphincter;
3. the absence of reflux.

Operation Technique

The operation is performed when the competence of the anal sphincter has been satisfactorily tested. In some cases it is necessary to wait until the child is 3 years old to ascertain that the sphincter is competent. Prolonged exposure of the exstrophied bladder mucosa will produce inflammatory lesions, fibrosis and damage the uretero-trigonal musculature which may later result in reflux or squamous metaplasia and glandular adenoma in which neoplastic changes might develop (Culp, 1964). The absence of reflux can be tested easily. A small glass funnel is firmly applied on the abdominal wall over the exstrophied bladder. The funnel is attached to a T-tube and through 1 of the arms contrast medium is injected under pressure with a syringe; a manometer is attached to the other arm to measure the pressure.

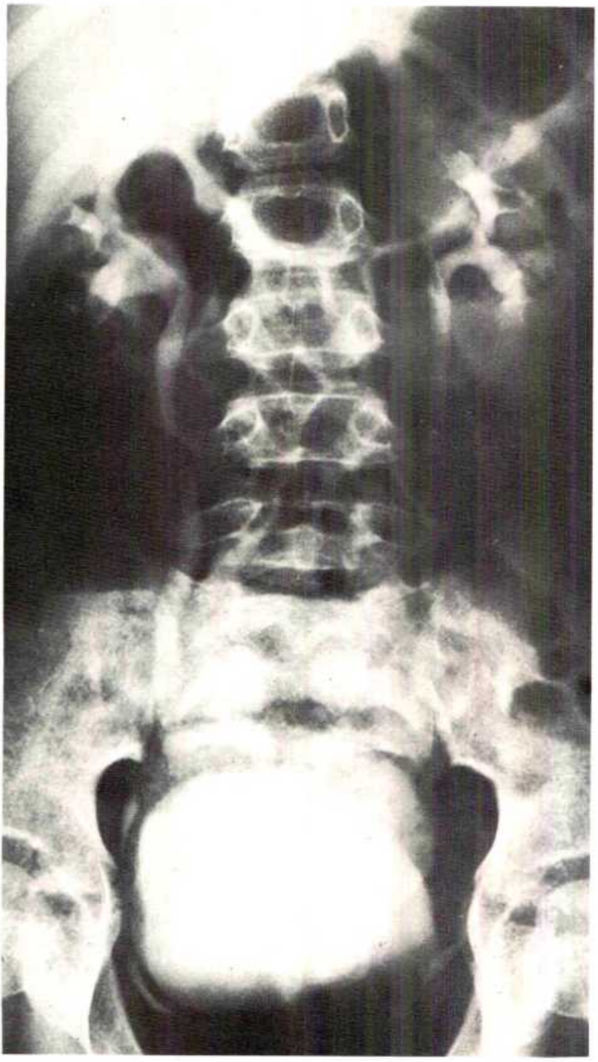

Fig. 1 Control IVP 8 years after trigonosigmoidostomy in a girl with bladder exstrophy operated at the age of 4 years. Normal renal function. No upper tract dilatation. Note that the sigmoid colon has taken the form of a "bladder".

The operation consists of the implantation of the vesical trigone in the sigmoid colon without any cutaneous diversion; the technique has been previously described in detail (Gregoir, 1968).

Results

Twenty-three patients have been followed from 3 to 19 years, the average period being 10 years. One patient from another country was lost to follow-up and 1 patient died in the post-operative period from rupture of oesophageal varices. In general, patients who developed complications have deteriorated within the first years after the operation. Patients who had a normal urogram, minor or no infection, and good electrolytic balance for a few years did not deteriorate subsequently.

Renal Function

The urogram has given the most valuable information in the post-operative follow-up. In 2 cases the urogram showed stones in the kidney and 1 of the stones caused ureteric obstruction. In another case bilateral hydronephrosis developed accompanied by severe parenchymal infection due to reflux. This case had had several unsuccessful attempts at reconstruction and was the first in this series; reflux had not been tested for before the operation and a cutaneous diversion had to be performed.

In all other 23 cases the urogram was satisfactory at repeated intervals.

Electrolytic Disturbances

About half of the patients showed transient elevation of the blood chloride and a lowering of bicarbonate. The remainder of the patients showed no electrolytic disturbances. These changes were insignificant in most cases and the patients remained asymptomatic. A few cases required corrective medical measures such as alkalinisation. About one-third of the infants developed abnormal thirst; they did not however show evident electrolytic disturbances or renal insufficiency. In all the 23 patients having a normal urogram, blood urea and creatinine were within normal limits.

Infection

The rate of infection and complications was surprisingly low and antibiotic medication was administered for only a short period. Prolonged medication was not necessary.

Operations for Complications

Two patients required an additional operation; 1 for an obstructive ureteric stone, the other for hydronephrosis and reflux underwent a cutaneous diversion.

Continence

During the day continence was perfect in all cases. During the night however most patients were incontinent for several months after the operation. This lasted for more than 5 years in 6 cases but finally disappeared in most of them.

As far as the sexual function is concerned most of our patients are still too young to be objectively evaluated, but some adults have married recently.

Overall Results

Failures

(1) One death: a 30-year-old alcoholic patient had a sudden rupture of oesophageal varices on the fifth post-operative day and died.

(2) One case was a complete failure as it required a secondary urinary diversion for severe pyelonephritis and hydronephrosis.

Satisfactory

Four cases were considered as satisfactory. Two had symptomatic electrolytic disturbances that required an alkali regime and 2 others developed stones requiring operative removal.

Good

Eighteen cases were considered as good. They were followed for a minimum of 3 years and for an average of 10 years. They were symptom free, the urogram remained normal, blood chemistry was within normal limits and they led a normal social life with normal life expectancy. The adults are gainfully employed and some of them are married. They are all perfectly continent although a few cases suffered from night wetting for some years before it finally disappeared.

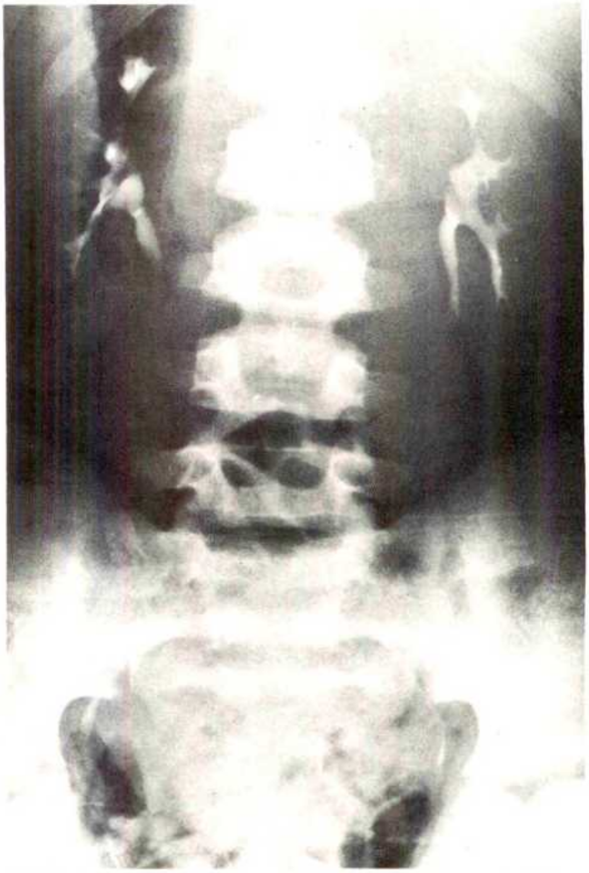

Fig. 2 Normal urogram 6 years after trigonosigmoidostomy.

Discussion

The basic principle that inspired Maydl (1894) to perform implantation of the trigone in the sigmoid colon in bladder exstrophy was to preserve intact the uretero-vesical junction so as to achieve better functional results than with a simple ureterosigmoidostomy. The present series seems to confirm this idea. Histological study of the uretero-vesical junction in bladder exstrophy has shown that the uretero-trigonal musculature is quite normal. The exstrophied bladder does not reflux. The normal antireflux function of the uretero-vesical junction is preserved in trigonosigmoidostomy if the trigone is normal before the operation and if its vascular and nervous supply is

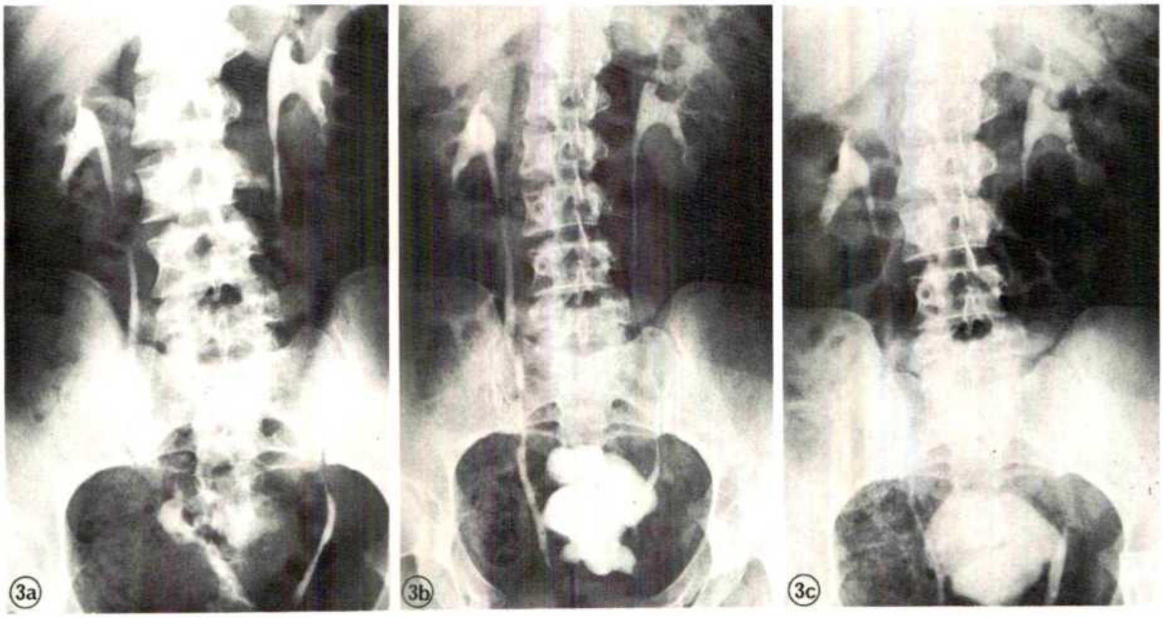

Fig. 3 Trigonosigmoidostomy for bladder exstrophy—control urograms: (a) 4 years later; (b) 14 years later; (c) 19 years later.

not jeopardised during the procedure. This antireflux mechanism deteriorates and disappears if prolonged exposure of the mucosa produces inflammatory lesions, fibrosis or squamous metaplasia that destroys the uretero-trigonal musculature. Several authors emphasise that reconstructed exstrophied bladders present a high percentage of reflux. In this instance however our opinion is that reflux is secondary to fibrosis and rigidity of the reconstructed bladder which may be of reduced capacity and the seat of severe chronic infection.

In about half of the cases (12) with trigonosigmoidostomy the injection of contrast medium in the rectosigmoid did not show reflux to the ureters. The others were not tested.

Primary reconstruction of the exstrophied bladder will always remain the theoretical ideal objective, but even in the experienced hand of surgeons with a special interest in the problem the success rate is small, serious complications such as hydronephrosis, severe pyelonephritis and stone formations are not rare and these children may undergo multiple operations with long hospitalisation and difficult social and psychological problems. For example Williams and Keeton (1973) reviewed 36 cases in their latest series and considered that 19 were reasonable candidates for primary closure, acceptable continence being obtained in 6. Marshall and Muecke (1970) had satisfactory results in 20% of their cases. Fisher and Retik (1969) reviewed 26 cases of which 9 were continent. Ezell and Carlsson (1970) had 19 patients of whom 9 were reconstructed and 2 achieved good continence. Cendron (1971) obtained acceptable continence in 6 of 12 children; reflux was present in 3 of these cases. Megalli and Lattimer (1973) reviewed 140 cases of exstrophy; primary closure was performed on 89 children of whom only 1 achieved successful continence, and 26 underwent subsequent diversion. Williams and Keeton (1973) consider that if functional reconstruction of the exstrophied bladder is to be considered some selection is important and that about 50% of cases may be considered as reasonable candidates for attempts at primary closure knowing that two-thirds of them will still need to be diverted. Marshall and Muecke (1970) are of the opinion that surgical closure of exstrophy of the bladder is still an investigative procedure worth consideration.

It is not our intention to claim that trigonosigmoidostomy in patients with bladder exstrophy is the ideal solution, but in our opinion it represents an acceptable compromise for this major urological malformation. The results of trigonosigmoidostomy seem more favourable than those

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obtained with a conventional ureterosigmoidostomy as far as renal function, infection and clinical status are concerned (Spence, 1966; King and Wendel, 1972; Bennett, 1973; Megalli and Lattimer, 1973). In this series, 75% of the patients have achieved an excellent result after a single operation and have met all Marshall's criteria for successful management of exstrophy.

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The Incidence and Consequences of Damage to the Parasympathetic Nerve Supply to the Bladder after Abdominoperineal Resection of the Rectum for Carcinoma

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Summary—Fifty-one patients undergoing abdominoperineal resection of the rectum for carcinoma were studied with regard to bladder function after surgery.

Fifty-nine per cent had motor denervation of the bladder due to tumour or operative damage to the pelvic parasympathetic nerves and this produced symptoms of incomplete bladder emptying requiring treatment in 90% of this group.

The factors affecting the incidence of nerve damage were discussed.

The long-term effect of parasympathetic nerve damage was investigated and the management is discussed.

Voiding dysfunction as manifested by varying degrees of incomplete bladder emptying has been noted to occur in 30 to 50% of patients undergoing abdominoperineal resection of the rectum for carcinoma (Lockhart-Mummery, 1932; Buckwalter *et al.*, 1955).

Originally mechanical problems such as the presence of the perineal pack, the change in the angulation of the bladder neck and latent prostatic obstruction were thought to be the main factors responsible. However, Watson and Williams (1952) suggested that there were 2 possible mechanisms—the majority due to bladder neck obstruction, unrelated to angulation; or rarely pelvic nerve injury, a concept endorsed by Ward and Nay (1972). Rankin (1969) and Fowler (1973) showed parasympathetic nerve injury to occur in 23 to 29% of patients and suggested this to be 1 of the main aetiological factors, a finding supported by the observation of Tank *et al.* (1972) who noted that the majority of urinary problems after abdominoperineal resection responded well to bethanechol. Watson and Williams (1952) described the anatomy of the pelvic parasympathetic nerves and indicated the possible site and mechanism of injury.

Little attention has been paid to the specific features of the rectal tumour which may contribute to the operative difficulty and/or to the need for wide excision, factors which obviously put the parasympathetic nerves at risk. Other problems following denervation, such as long-term morbidity and the effect on prognosis, have not been investigated in the past.

Material and Methods

Fifty-one patients have been fully evaluated with regard to bladder function following abdominoperineal resection for carcinoma in the period 1972 to 1975. Post-voiding difficulty was the main reason for referral for assessment, the minority being seen for routine post-operative evaluation.

The method of presentation of the patient and pre-existent urinary troubles were noted. The operative details were studied and the method of perineal wound treatment noted.

Bladder function was assessed by cystometry (Fowler, 1973) and where abnormal, this was repeated at 1 week, 1 month and 3 months thereafter for 1 year. Residual urine estimation was carried out daily until satisfactory voiding was established or surgical correction undertaken.

The rectal tumour was staged by Duke's method

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and the histological grade after Bröder. The position of the tumour on the circumference of the bowel and its distance from the anal margin was noted. The patients were divided into 2 groups—those with normal and those with altered bladder innervation respectively. The 2 groups were then compared in order to see whether any specific prognostic features emerged leading to the likelihood of bladder denervation.

Results

Of the 51 patients studied 36 were male and 15 female, with an average age of 62 years. All patients were followed up for a minimum of 6 months.

Pre-operative Urinary Symptoms

Seven patients had significant bladder symptoms pre-operatively: 3 had prostatism, 2 infection and 2 haematuria. Forty-nine of the 51 patients had a normal blood urea. Twenty-seven patients had pre-operative intravenous urograms carried out, significant abnormalities being noted in 7. These consisted of incomplete emptying (4) and obstructive uropathy (3).

Post-operative Cystometry

Thirty-seven of 51 patients had abnormal cystometry on the first evaluation, usually carried out within 7 days of operation. Seven had transient abnormalities, 5 being of motor loss and 2 of sensory loss. These 7 patients recovered normal bladder function in periods of time varying from 1 week to 6 months post-operatively leaving 30 of the 51 patients with residual permanent nerve damage.

Post-operative Urinary Symptoms

Thirty-five of 51 patients had either significant voiding difficulty or high residual urine volumes, in the period up to 6 months post-operatively. Ten of the 21 patients with normal bladder innervation had significant voiding difficulty compared with 25 of the 30 with cystometric abnormalities. Of the 10 patients having symptoms with normal cystometrograms, 7 required operative relief by transurethral prostatectomy in the male or urethrotomy in the female. Of the 25 patients having symptoms with denervated bladders on cystometry, 12 were managed by drugs alone, 3 had operation alone and 10 required both operation and drugs. No attempt was made to give drug treatment to those with normally innervated bladders, the dangers of cholinergic therapy in the presence of bladder outlet obstruction being well recognised.

The patients whose bladder denervation was detected routinely were not subject to over distension of the bladder and all retained a degree of bladder sensation. This was of a sensation of pressure. All remarked that feeling was present but that it was unaccompanied by pain even on cystometric filling, and this was totally unlike the normal bladder sensation. This group were all rehabilitated without difficulty and voided either when the altered sensation was present, or 3 hourly, whichever was the sooner. The patients were all instructed to strain once voiding had commenced.

Those patients referred because of post-operative difficulty had been subject to over distension for varying periods of time. Two patients, 1 male and 1 female, required permanent catheter drainage following failure of all conventional means, and 1 male patient subsequently required catheterisation because of incontinence following a second transurethral resection for high residual urines.

Pathological Stage/Grade of Tumour and Cystometric Findings (Table 1)

Those patients with invasive and more highly malignant tumours tended to demonstrate motor denervation more often than those with well differentiated or non-invasive tumours.

Table 1 Pathological Stage/Grade of Tumour and Cystometric Findings

	Duke's stage					*Bröder grade*			
	A	*B*	*C*	*D*	*NK*	*Well d.*	*Mod. d.*	*Poor d.*	*NK*
Normal innervation	5	4	3	4	5	11	2	3	5
Motor denervation	1	12	11	2	4	12	8	5	5
Total	6	16	14	6	9	23	10	8	10

Table 2 Circumferential Position of Tumour and Cystometric Findings

	Ant.	*Ant./lat.*	*Lat.*	*Post/lat.*	*Post.*	*Encl.*	*NK*
Normal innervation	10	2	3	1	0	2	3
Motor denervation	2	4	1	0	12	4	7

Circumferential Position of Tumour and Cystometric Findings (Table 2)

Patients with anteriorly placed tumours have the lowest rate of motor denervation of the bladder and those with posteriorly placed tumours, the highest rate. The tumours encircling the bowel and involving the posterior surface therefore fall into the posterior category.

Distance of Tumour from Anal Verge and Cystometric Findings (Table 3)

The rate of motor denervation appeared to relate more to the circumferential position of the tumour than to its distance from the anus.

Table 3 Distance from Anal Verges and Cystometric Findings

	0 to 4 cm		4 to 8 cm		8+ cm	
	Inn.	*Den.*	*Inn.*	*Den.*	*Inn.*	*Den.*
Ant.	1	–	5	1	4	1
Lat.	1	–	4	3	1	2
Post.	0	2	0	8	0	2
Incl.	0	0	1	2	1	2

NK—3 innervated, 7 denervated.

Operative Factors and Cystometric Findings (Table 4)

Motor denervation occurred more frequently in those patients where the coccyx was not excised and where the perineal wound was left open.

Table 4 Operative Factors and Cystometric Findings

	Coccyx excised			*Perineum closed*		
	Yes	*No*	*NK*	*Yes*	*No*	*NK*
Normal innervation	3	14	4	12	5	4
Motor denervation	3	23	4	12	14	4

Cystometric Findings and Prognosis

All deaths in this series have occurred within 4 years of operation. Five of 21 patients with normal bladder innervation died within 4 years compared with 8 of 30 patients with abnormal bladder function. However, those with intact bladder function post-operatively died of advanced tumour with no contribution in morbidity or mortality from the GU tract. Of those with denervated bladders however, 5 of the 8 patients who died had significant GU pathology, the most common being cystitis and suppurative pyelitis (5 patients) and 1 patient died of pulmonary embolus following a prostatectomy.

Discussion

The group of patients studied, although not a consecutive series, appears to be a fair representation of all grades of carcinoma of the rectum and the survival rates obtained closely match those of other reports (Goligher, 1975). The incidence of motor denervation of the bladder in our group is higher at approximately 59% because of the selective nature of the referral compared with other reports for a consecutive series, *e.g.* 23% (Rankin, 1969).

Ten of the 21 patients with normal post-operative bladder innervation required treatment because of urinary symptoms. This reflects the incidence of latent bladder neck obstruction in both sexes in this age group. It also supports the contention that the various mechanical factors stressed by earlier authors are pertinent. Twenty-five of the 30 patients with altered bladder function required treatment to establish acceptable voiding—12 by drugs alone and 13 by operation and/or drugs. The increased incidence in this latter group with denervated bladder underlines the importance of nerve injury in the pathogenesis of voiding dysfunction. It was interesting to note that recovery occurred in 7 patients who had cystometric abnormalities initially, indicating partial nerve injury or neuropraxia. However, it is possible that pelvic infection may serve to destroy nerves which would otherwise have recovered, as shown by the rate of denervation among those patients where the perineum was left open and therefore more liable to infection.

The routine use of the intravenous urogram pre-operatively would effectively detect patients with significant bladder neck obstruction or more importantly ureteric obstruction indicating an invasive tumour. Lower urinary tract obstruction was noted in 5 patients on pre-operative IVP, 3 of whom had improved function post-operatively (this phenomenon has previously been reported by Watson and Williams, 1952) and 2 required prostatectomy.

Pre-operative cystometry is of value not only in assessing the stage of the tumour as indicated by alteration of the bladder reflex arc with posterior penetrating tumours, but also in detecting small changes post-operatively indicative of isolated or sub-total nerve injury.

As would be expected, there is an increased incidence of denervation in those patients with invasive or highly malignant tumours, a finding at variance with that of Tank *et al.*, 1972. The most critical factor in predicting denervation was the circumferential position of the tumour, those situated posteriorly or encircling the bowel having a much higher incidence of bladder dysfunction. The distance of the tumour from the anal verge did not appear to be of any significance.

The failure to identify the correct plane of dissection in front of the sacrum would appear to be the most likely mechanism of injury. Transgression of this plane may be inevitable in the pursuit of cure, or when inflammatory oedema has rendered the pre-sacral nerves brittle, especially in the case of posterior growths. There is an increased incidence of denervation in those patients whose coccyx was left *in situ* and where the perineum was left open, suggesting that restriction of access and infection may be important.

The consequence of denervation in the immediate post-operative period and also in the long term are related to the accumulation of large volumes of residual urine and subsequent bladder atony. Should this occur early in the post-operative period and pass unnoticed, then rehabilitation of the bladder may be difficult, requiring prolonged drug regimens which are unpleasant for the patient and the surgeon alike. Restoration of normal voiding may be impossible where retention has been severe. Even when this is recognised, severe morbidity or even mortality can result, as shown by the fact that 5 of the 8 patients who died having denervated bladders had significant episodes of lower urinary infection and evidence of suppurative pyelonephritis at post-mortem.

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Experience with Anteromedian (12 O'Clock) External Urethral Sphincterotomy in 100 Male Subjects with Neuropathic Bladders

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Summary—One hundred male spinal cord injured patients have now undergone anteromedian (12 o'clock) external urethral sphincterotomy alone or in combination with transurethral incision or resection of the bladder neck.

The functional effect of this procedure has been documented by voiding cystourethrogram and urodynamic studies.

The morbidity and clinical results including blood loss and loss of reflex erections are reviewed.

The short-term clinical results suggest that this is the best of currently available techniques to lower external urethral sphincter resistance.

External urethral sphincterotomy is a well accepted and widely practised therapeutic procedure in selected male patients with neurogenic bladder dysfunction. A variety of techniques for accomplishing the desired result of an infection-free patient with low residual urine volumes and urodynamic stability have been described (Ross *et al.*, 1967; Schellhammer *et al.*, 1973; Madersbacher and Scott, 1975; Kiviat, 1975).

We have previously published data on 84 patients having external sphincterotomy which favours the anteromedial (12 o'clock) incision as opposed to other techniques, in particular using bilateral incisions at 3 and 9 o'clock (Yalla *et al.*, 1977a). We have now used the anteromedial sphincterotomy on 100 male patients with neurogenic vesicourethral dysfunction. The results in this updated series impressively support our initial enthusiasm for this procedure.

Patients and Procedure

This series is comprised almost exclusively of male spinal cord injury patients, who have been referred to the Veterans Administration Hospital system. Sexual histories were taken and observations of penile erections were made during a period of intermittent catheterisation prior to sphincterotomy and post-operatively. Each patient had pre-operative and some post-operative cystosphincterometric studies, pressure monitored voiding cystourethrograms and urethral pressure profiles using techniques described previously (Yalla *et al.*, 1975, 1976).

Indications for sphincterotomy included large residual urine volumes with or without infection, vesicoureteric reflux, marked anatomical changes in upper or lower urinary tracts, bladder associated autonomic dysreflexia and urodynamic results indicating detrusor-striated sphincter dyssynergia.

Anteromedian sphincterotomy was performed under direct vision using the Storz electroknife and 30° lens. Multiple shallow strokes were taken at the 12 o'clock position extending from just distal to the bladder neck into the bulbous urethra. The amount of functional striated sphincter component in the supra-montane prostatic urethra indicated by the urodynamic evaluation determined the approximate site at which the anteromedian incision was commenced (Yalla *et al.*, 1977b). The cut was deepest in the membranous urethra and clearly extended into but not through the capsule of the prostate, entirely through the membranous urethra and into the spongy tissue of the bulbous urethra. At the conclusion of the procedure any arterial bleeders were easily fulgurated. Emphasis was placed on being able to visualise the dark cavern

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of the bladder with the scope in the proximal bulbous urethra. We were often able to see the retracted edges of the external sphincter muscle tissue which were withdrawn more than 90° on each side of the midline. Also visualised with some frequency were what, by size and location, were judged to be the major tributaries of the deep dorsal vein of the penis. A 24F 3 way Foley catheter with 30 to 40 ml in the balloon was inserted and gentle traction applied if necessary for suitably clear effluent. The catheter was left in place for 2 to 5 days.

Results

Our results in 100 patients having anteromedian external sphincterotomy alone or in combination with TUR are listed in Table 1. They are compared with our own results using the 3 and 9 o'clock bilateral incision, as well as other published series where attention was given to preservation of erections and post-operative haemorrhage. There was significantly less morbidity using the single anteromedian incision when compared to 3 and 9 o'clock bilateral incisions in our series. This is evident both in the incidence of haemorrhage as well as loss of erections. When compared with data from the other published series (listed in Table 1) these findings are evident throughout.

Discussion

It has been our experience over the past several years that the spinal cord injury patients as a group have become increasingly conscious of their sexuality as well as their right to question the indications and outcomes of recommended surgical procedures. In particular, the youthful male population is attuned to any ability it may have to generate reflex or psychogenic erections. Because of this, any procedure which threatens this ability is met with justified resistance.

We have been delighted with the anteromedian technique of sphincterotomy. We feel justified, at this time, in advertising it to our patients as a low risk procedure which, except for the desired urodynamic changes, will leave their physiology unaltered. Also, as previously reported by ourselves and others, the urodynamic results are at least equal to those achieved with other methods (Madersbacher and Scott, 1976; Yalla *et al.*, 1977a).

Contrary to most other authors who recommend a bilateral sphincterotomy, we support the contention of Madersbacher and Scott (1976) that the anteromedian incision is sufficient and measurable. Oelrich (1964) and Sant (1972) have demonstrated that the circular striated muscle fibres around the membranous urethra and the longitudinally oriented fibres of the external

Table 1

Reference	*Total No. of patients*	*No. with erection pre-operative*	*Partial loss of erections post-operative*	*Complete loss of erections post-operative*	*Total No. of patients in loss of erections*	*Haemorrhage requiring transfusion post-operative*
Schoenfeld *et al.* (1974) 3 and 9 o'clock (resection)	25	22	3 (14%)	5 (23%)	8 (36%)	Not reported
Kiviat (1975) 3 and 9 o'clock (incision)	17	15	6 (40%)	5 (33%)	11 (73%)	4 (23%)
11 and 1 o'clock	16	14	1 (7%)	0	1 (7%)	1 (7%)
Crane and Hackler (1976) 3 and 9 o'clock (incisions)	129	101	16 (16%)	2 (2%)	18 (18%)	Not reported
Madersbacher and Scott (1976) 12 o'clock (incision)	35	Not reported	Not reported	Not reported	Not reported	0
Present series						
3 and 9 o'clock (incision)	53	28	4 (14%)	2 (7%)	6 (21%)	5 (8%)
12 o'clock	100	62	0	0	0	0

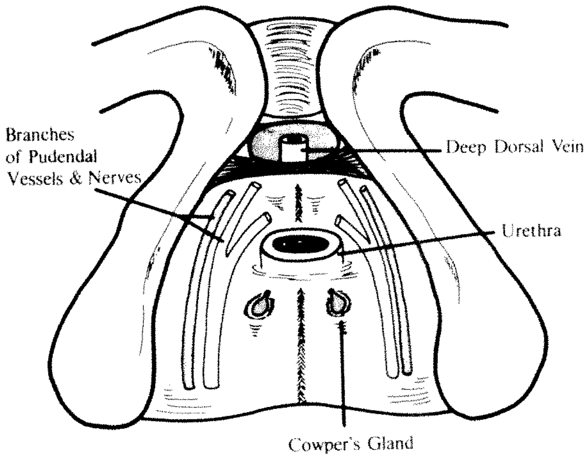

Fig. 1 Structures in relation to membranous urethra in the urogenital diaphragm. The urethra is shown surrounded by a sheet of striated muscle—external sphincter.

sphincter are greatest anteriorly. Also, the neurovascular anatomy of the urogenital diaphragm clearly shows the bilateral course of the internal pudendal vessels and nerves at this level (Fig. 1). In this setting, it seems logical to cut the external sphincter in the midline anteriorly, where it is strongest, and there is least chance of significant neurovascular injury. The empirical findings of haemorrhage and loss of erections following lateral incisions are commanding evidence of the functional anatomy of this area.

In our series the urodynamic results of the anteromedian external sphincterotomy are at least as good as those recorded using the 3 and 9 o'clock incisions. In addition, contrary to early thinking and admonition we have found morbidity from haemorrhage to be considerably less. Finally, although the data on post-sphincterotomy erectile impotence is still being gathered, the anteromedian technique clearly offers a very low if not zero incidence of this significant complication, which is known to plague other methods. Hence, we believe that the anteromedian sphincterotomy should replace other methods as primary treatment in appropriately selected patients.

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The Management of Indwelling Catheters

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Summary—Eighteen geriatric patients with indwelling catheters were observed for a total of 393 weekly urine specimens. The effects of a 1 week course of antibiotics/chemotherapeutic agent followed by urinary antiseptics for 6 weeks, and also of regular bladder washouts, were noted.

All urine specimens were infected except 24% during antibiotic treatment and 9% during antiseptics and 6% after washouts. Only washouts reduced the extent of catheter blockage.

There was little difference in the time *in situ* between silastic and latex Foley catheters—only 31% of silastic remaining for longer than 4 weeks. Bard-Roberts catheters were the least satisfactory. Catheter leakage was not affected by urinary pH.

Further developments in long-term catheter management are needed.

Although much has been written about the use of indwelling catheters left *in situ* from 1 to 7 days, usually following prostatic or gynaecological surgery, there has been little critical observation about the management of catheters which are left in the bladder on a permanent or semi-permanent basis. Catheters are used in this way for the management of incontinence in 2 main groups of patients—paraplegics and the aged suffering from intractable incontinence. Attempts to prevent or eradicate the infection accompanying long-term indwelling catheterisation are generally unrewarding, but data available to support such contentions are scarce. Similarly, there is little published comparison between different types of catheters.

Indwelling catheters may be used for 2 types of incontinence—that associated with recurring chronic retention and overflow (the atonic bladder) and that associated with uncontrollable uninhibited bladder contractions (the reflex and uninhibited neuropathic bladders and some unstable bladders).

The use of oral urinary antiseptics to diminish infection and prevent catheter blockage has been described by Norrman and Wibell (1976). Antiseptics may also be used as instillations or washouts. Only the intermittent instillation of antiseptic is feasible in patients with long-term indwelling catheters. Zinner *et al.* (1970) and Abramson and Feibel (1974) indicated that continuous rinsing bathed only the mucosal area nearest the tip of the catheter, whereas intermittent filling bathed the whole of the bladder except the part on which the Foley balloon was resting. Solutions such as neomycin, chlorhexidine and noxithiolin (Horsfield, 1967) have all been used for this purpose. The possibility of chemical cystitis arises with regular washouts (Harper and Matz, 1975).

Two main variations of the Foley catheter are a silicone coating to prevent crystal encrustation and the addition of drainage eyes immediately below the balloon as well as above it (Roberts, 1969).

The present study was undertaken to determine the facts about urinary infection with long-term catheterisation; to note the effect of antibiotics, long-term urinary antiseptics and bladder washouts; to compare different types of catheters and to identify problems in catheter management.

Patients and Methods

Long stay geriatric patients with indwelling catheters were seen at weekly intervals to record whether the catheter had been changed during the previous week, whether any drugs affecting urinary infection had been given, whether any washouts had been given, which type of catheter had been inserted and whether there had been any side-effects.

A sample of urine for culture was taken through the catheter by clamping it and after a variable period of time removing the end from the

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drainage bag and collecting urine direct from the catheter.

After an initial period of observation, treatment with an appropriate antibiotic was given for 1 week, followed by treatment with hexamine hippurate 1 g twice daily for 6 weeks.

Results

Urinary Infection

Eighteen patients were studied, 5 for 8 to 12 weeks, 6 for 13 to 20 weeks and 7 for 31 to 47 weeks. Altogether 393 specimens were cultured and 20 (5%) found sterile; 311 (79%) gave a single organism and 62 (16%) a mixed culture (Table 1).

Fifteen patients completed a 6 week course of hexamine hippurate. In 2 cases it was stopped because of nausea at the end of 3 and 4 weeks respectively and the 18th patient in the study died before it was given. Of the 15 patients treated with hexamine hippurate 14 were given a 1 week course of the appropriate antibiotic or chemotherapeutic agent (co-trimoxazole 8, nitrofurantoin 3, ampicillin or gentamicin 2, nalidixic acid 1).

Table 1 Organism Grown in 393 Specimens of Urine from Catheters

Organism	*Type of infection*
	Single organism grown
Coliform	39%
Proteus	27%
Providentia	8%
Pyocyaneus	5%
Other	21%
Total number	311 (100%)
	Mixed infection
Coliform + Proteus	47%
Coliform + others	29%
Other mixtures	24%
Total number	62 (100%)

Of the 20 sterile specimens obtained 4 were during treatment with antibiotic, 9 with hexamine hippurate and 11 following bladder washouts with noxythiolin. From a total number of 17 specimens obtained while patients were on antibiotics 4 were sterile. Similarly out of 101 specimens obtained during hexamine hippurate therapy, 9 were sterile and of 119 specimens following bladder washout within the previous week 7 were sterile.

Type of Catheter and Reason for Change

Table 2 indicates the type of catheter used, the period each catheter remained *in situ* and the reason for changing it. There were no differences in the reasons for changing silastic and latex catheters. For each type just under one-third were routine changes and two-thirds were due to leakage alongside the catheter. One-third of the Bard-Roberts catheters were removed for leakage and one-third fell out, were pulled out or were uncomfortable.

There was little difference in the length of time that any type of catheter remained *in situ*. Sixty-nine per cent of the silastic and 85% of the latex catheters had been removed by the end of 4 weeks. However, two-thirds of the 16 Bard-Roberts catheters were removed after only 1 week.

Leakage

Only 4 of the 18 patients had no leakage alongside the catheter (including the only male in the trial). In the remaining 14 the extent of leakage during the period without treatment was compared with the period on hexamine hippurate. The same comparison was made in relation to washouts. Table 3 shows no difference with hexamine hippurate but an inverse relationship between the number of bladder washouts and the amount of leakage—the more washouts, the less leakage.

Table 2 Types of Catheter Used

Catheter	*Reason for change*			*Period* in situ *(weeks)*				*No.*
	Routine	*Leakage*	*Pulled out*	*1*	*2-4*	*5-10*	*11+*	
Silastic	32%	61%	7%	17.0%	52%	28%	3.0%	60 (100%)
Latex	32%	65%	3%	24%	61%	15%	-	34 (100%)
Bard-Roberts	31%	31%	38%	62.5%	37.5%	-	-	16 (100%)

Table 3 Comparison of (*a*) Quantity of Leakage; with (*b*) Quantity of Leakage when on Hexamine Hippurate; and (*c*) with Percentage of Washouts Given

Patient No.	*Leakage (%)* (*a*)	*Leaking while on hexamine hippurate (%)* (*b*)	*Washouts (%)* (*c*)
7	52	83	4
4	43	33	53
11	32	17	3
6	31	0	3
10	30	17	15
3	25	25	25
16	23	17	13
2	20	17	30
1	19	0	47
5	14	17	16
14	13	66	48
15	13	17	48
17	13	0	17
8	8	17	36
9	0	0	83
12	0	0	0
13	0	0	95
18	0	0	76

* Spearman rho non-parametric correlation coefficient:

Columns (*a*) v. (*b*): rho = 0.59, t = 2.93, 16 df $P < 0.01$

direct correlation—hexamine makes no difference to proportion leaking.

(*a*) v. (*c*): rho = −0.49, t = −2.25, 16 df $P < 0.05$

Indirect correlation—the more washouts the less leakage.

(% refers to observations).

Table 4 pH of Urine (% During Weeks on Different Types of Treatment)

pH	*6*	*7*	*8*	*9*	*No.*
No treatment	48	25	7	20	124 (100%)
Washout	45	41	8	6	98 (100%)
Hexamine hippurate	65	30	1	4	70 (100%)
Antibiotic	94	6	-	-	18 (100%)

The urinary pH while on treatment with various agents is shown in Table 4. Only 27% of the patients show a pH of 8 or more during the untreated period and the proportion of pH 6 increases with washouts, hexamine hippurate and antibiotics. Hexamine hippurate showed less acid reaction (64%) than the antibiotic group (94%).

There was no demonstrable relationship between leakage and pH. Using the Spearman rho non-parametric correlation coefficient between rank order of percentage of leakage and mean pH, $P < 0.2$. The overall mean pH during non-leaking observations was 6.9, and during "leaking" observations 7.0.

Discussion

The present findings show no useful effect in preventing infection using continuous hexamine hippurate or washouts with noxythiolin (only 9% and 6% of specimens were sterile with either regime). A 1 week course of antibiotics produced 24% sterile specimens. Clearly none of these methods is worth using to try and control infection—and in geriatric patients with intractable incontinence requiring continuous catheterisation infection does not seem to be a serious matter in the very limited life expectancy such patients have. Norrman and Wibell (1976) used hexamine hippurate 1 g twice daily in 22 female patients with indwelling catheters. They showed no effect on bacteriuria. There was less "clinical infection" during the treatment period but conversely there was more pyrexia of unknown origin. They did show benefit from continuous hexamine hippurate in preventing catheter blockage. The present study does not confirm this although it shows that regular washouts diminish the extent of leakage alongside the catheter. Leakage was not affected by pH of urine.

There is little difference in the length of time between changes when comparing latex with silastic catheters. Two-thirds of the silastic catheters were not left *in situ* for a length of time that would justify their use. They were removed because of leakage around the catheter presumably due to encrustation or to kinking of the catheter outside the bladder or obstruction of the flow of urine because of insufficient emptying of the bag. In the latter cases clearly the reported advantages of the silastic catheter are not having an opportunity to become apparent.

The purpose of the silicone coated catheters is to prevent encrustation. Bruce and Clark (1974) compared encrustation in geriatric patients with latex and silicone coated catheters, and found that while it occurred in both, the amount was considerably less in the same patients in a similar period of time, with the silicone coated catheters. They also found marked variations between different patients' susceptibility to encrustation, and no direct relationship between the amount of encrustation and the time the catheter was *in* *situ*. Wastling (1972) has reported on the introduction of silastic catheters in a group of 7 male patients on long-term catheterisation. Six catheters blocked within 3 weeks and the seventh lasted for 3 months. However, 2 years later Wastling (1974) reported 15 patients in whom silastic catheters had been used exclusively and in these the average time *in situ* was 5 months (with a range from 2 to 9 months). This suggests that with management supervised by a highly motivated nurse the problems of leakage can be overcome. Altogether he observed the use of 74 individual silastic catheters. Ten of the 17 patients were taking intermittent urinary antiseptics by mouth and a further 3 continuous antiseptics by mouth. He suggests a limit of 6 months for 1 silastic catheter.

Wastling reported that 49 of the 74 changes were because of blockage, including 1 patient whose catheter blocked 15 times. He suggested that in a patient whose catheter blocks, this will continue to happen whatever type of catheter is used. This suggestion that certain individual patients have a higher susceptibility to catheter blockage is borne out by Bruce and Clark (1974) who showed that encrustation had no direct relationship with time but rather with individual patients' susceptibility, probably related also to the susceptibility of patients to form bladder calculi. The present study bears out this observation, as in 4 patients no leakage occurred, while in 6 leakage occurred with 30% or more of catheters.

The Bard-Roberts catheter (Roberts, 1969) was the least successful of all because of the small size of the balloon (5 ml) and because the eyes below the balloon cause discomfort.

The present investigation probably reflects a typical situation in geriatric wards. Better methods of managing silastic catheters must therefore be found if their extra cost is to be justified. This means further methods of avoiding encrustation—and of diminishing the likelihood of obstruction by kinking. Since obstruction seems less common in male patients it may be that a short female Foley catheter will have an advantage for long-term use. No advantage is apparent in the use of continuous urinary antiseptics, or short course antibiotics, although washouts do diminish leakage. The present findings do not support any relationship between urinary pH and catheter leakage.

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Diagnostic Catheterisation and Bacteriuria in Women with Urinary Incontinence

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Summary – The risk of single catheterisation in females with urinary incontinence and/or genital prolapse was studied in patients referred for urodynamic examination.

Two hundred and eighty-six single catheterisations were performed followed by a mid-stream specimen 1 week later, and in 31 of these the initial specimen contained more than 10^5 bacteria.

Following catheterisation bacteriuria occurred in 5 (2%) of the patients with initially sterile urine.

The phenomenon of "asymptomatic bacteriuria", "transient significant bacteriuria" and "bladder defence mechanism" is discussed.

The risk of introducing urinary tract infection in urodynamic studies is low.

Urinary tract infection following single catheterisation occurs with an incidence of 1 to 15% (Kass, 1962; Turck *et al.*, 1962). Stamey (1973) has shown a correlation between the bacterial colonisation of the vaginal introitus and urinary tract in women and Cox (1966) has demonstrated great numbers of bacteria in the urethra even in its proximal part just below the bladder neck.

The normal female bladder is not necessarily sterile, but may be intermittently infected by significant numbers of bacteria (Scardino *et al.*, 1973).

Apart from catheterisation, Kass (1962) has found the prevalence of bacteriuria in 3029 females to be 4% with a range from 2% in young women to 15% after the menopause.

A large number of patients have to be catheterised in urological and gynaecological departments in order to diagnose vesical and intravesical disorders. Females with urinary incontinence may be subjected to cystoscopy, cystometry, urodynamic and uroradiological examinations.

The aim of the present study was to delineate the risk of catheterisation associated with urodynamic investigation in females with urinary incontinence and/or genital prolapse.

Material and Methods

All patients referred to the Department of Gynaecology and Urology for urinary incontinence and/or genital prolapse during a 2-year period underwent urodynamic investigation. Three hundred and sixty-nine females with a mean age of 53.7 years (range: 19 to 82) were examined. In 286 females, urine cultures were performed at the time of the initial catheterisation as well as 1 week later.

The urodynamic examination consisted of medium filling water cystometry followed by urinary flow recording with simultaneous recording of vesical and rectal pressures and electromyography from the sphincter apparatus (Olesen *et al.*, 1975). The voiding and pressure-flow-EMG recordings were repeated 4 or 5 times to obtain reproducibility.

The examinations were performed on out-patients. Immediately before the cystometry a urethral catheter (Chs. 16 to 18) was introduced under sterile drapes by one of the authors (S.W.). The area around the external urethral meatus was cleaned with chlorhexidine 0.02% and the urethra was disinfected with chlorhexidine gel 0.1%. Sterile rubber gloves were used to handle the catheter. The bladder was emptied and the urine sent for bacteriological examination. After cystometry, a suprapubic catheter (Ch. 3.5) was inserted into the bladder using a sterile technique and the transurethral catheter removed. The vesical pressure was measured and the bladder filled through the suprapubic catheter during the urodynamic investigation. Follow-up urine specimens were obtained 1 week later. A clean voiding technique with collection of a mid-stream specimen was used.

All urine specimens were promptly cooled to 4°C and sent to the bacteriological laboratory. The samples were cultured quantitatively using calibrated loops (Vejlsgaard, 1973). Bacteriuria was defined as the occurrence of at least 100,000 bacterial colonies per ml urine.

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Table 1 Bacteriuria following Single Catheterisation in Female Out-patients with Urinary Incontinence and/or Genital Prolapse

Number of urine specimens	*Number of urine specimens with 10^5 bacteria per ml*	
	Initial urine specimens at catheterisation	*Mid-stream urine specimens 1 week after catheterisation*
28	28	28
2	2	0
1	1	0
5	0	5
250	0	0

* Treated with antibiotics.

Results

The incidence of bacteriuria following a single catheterisation is summarised in Table 1. Bacteriuria was found in 31 urine cultures at the initial catherisation, and the same organisms were found 1 week after the urodynamic examination in a mid-stream specimen in 28 patients. Two patients were treated with antibiotics with effect, and 1 patient who was infected with a significant growth of *E. coli* in the initial specimen had no growth in the urine at the follow-up. Five patients with initially sterile urine had significant bacteriuria 1 week later (2%). They had few symptoms such as dysuria and frequency and were treated with antibiotics with good effect. Sulphamethiazole was the agent usually used. None had signs of upper urinary tract infection with fever and flank pain. One of these patients may have harboured the organism in the urinary tract prior to the catheterisation since she had been treated several times for urinary tract infection with the same bacterial strain. Two hundred and fifty patients had sterile urine both at the time of the catheterisation and 1 week later.

Discussion

The urethra in healthy young women represents an inadequate barrier to bacterial invasion, and the bladder urine is frequently colonised by significant numbers of bacteria, a phenomenon which Scardino *et al.* (1973) have termed "transient significant bacteriuria". However, the bladder mucosa is known to affect bacterial growth. Cox and Hinman (1961) have demonstrated this "bladder defence mechanism", and Parsons *et al.* (1975) in an experimental study and Mooney *et al.* (1976) in an electron microscopic study have also supported this observation. Cox (1966) demonstrated a large number of bacteria just below the bladder neck so that when a catheter is introduced into the bladder through the urethra, there is a great risk of introducing bacteria in a magnitude with which the individual defence mechanism—good or bad—cannot cope.

By employing a careful aseptic technique of catheterisation, disinfection of the urethra with chlorhexidine gel, it is possible to reduce the frequency of infection to one-third (Gillespie *et al.*, 1962). The frequency can be further decreased by using the funnel technique described by Sood (1972).

The incidence of iatrogenic bacteriuria (2%) in this material is low and some of the infections perhaps represent "normal" asymptomatic bacteriuria or transient significant bacteriuria which become symptomatic after the manipulation with the catheter. The urodynamic investigation in females with urinary incontinence is useful, and using Gillespie's technique of catheterisation there is only little risk of infection in these patients. However, there has to be a clear indication for these investigations and all patients must have a mid-stream specimen urine culture 1 week after the examination.

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Should Patients be Shaved Prior to Transurethral Surgery?

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Summary—In a prospective randomised trial no significant difference in urinary infection was found when routine pubic shaving prior to transurethral surgery was compared with no pubic shave. An argument based on financial and aesthetic considerations is presented to support the abolition of this traditional policy.

Hair, the effects of its presence and its removal from the operative site by shaving or depilation, have been well documented (Powis *et al.*, 1976; *British Medical Journal*, 1976; Seropian and Reynolds, 1971). The main reason for shaving is to avoid the introduction of bacteria which may result in a urinary tract infection. Since we could find no information to support the practice of complete pubic shaving prior to transurethral surgery a prospective randomised trial was arranged to assess the risks of urinary tract infection following the operative procedure.

Patients and Methods

One hundred patients admitted electively for transurethral resection were allocated pre-operatively by random card selection into either "shaved" or "unshaved" groups. Some patients were subsequently excluded because of pre-operative urinary infection, change of planned operation or incomplete bacteriological studies. These patients were reallocated randomly leaving 2 equal groups for comparision.

All patients on admission supplied a mid-stream specimen of urine (MSSU) for bacteriological examination. Patients allocated to the "shaved" group were shaved on the day before surgery (18 to 24 h pre-operatively). Transurethral surgery was performed under the care of 2 consultant urologists in general surgical theatres where strict aseptic techniques were used. Hibitane solution was used for skin preparation.

Following transurethral resection the bladder was drained by a closed system using continuous irrigation until the risk of clot retention was past. When the drainage appeared clear of blood a catheter sample of urine (CSU) was taken for bacteriological examination and the catheter removed. Due to the resection procedure all the catheter samples of urine contained varying numbers of both red and white blood cells. Prophylactic antibiotics were not used.

The criterion of infection was 10^5 or more organisms per ml of urine. Twenty-two patients had a bladder tumour resected and 78 had resection of either a benign hyperplasia or carcinoma of the prostate gland.

Table 1

	Shaved n = 50	*Unshaved* n = 50
Uninfected (CSU)	43	44
Infected (CSU)	7 (14%)	6 (12%)

Results

The table shows the number of infections and there is no significant difference between the 2 groups. No significant difference in infection rates was noted between the different diagnostic groups.

Discussion

This simple study indicated that the policy of shaving patients in order to reduce the risk of urinary tract infection during transurethral resection is unjustified.

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Shaving is an expensive (Powis *et al.*, 1976) and mildly mutilating (*British Medical Journal*, 1976) ritual which does not confer any advantage to either patient or surgeon. Although hair has been noted to be a potential source of pathogenic bacteria (Summers *et al.*, 1965; Dineen and Drusin, 1973), shaving or depilation may merely alter the bacterial population (Powis *et al.*, 1976; Seropian and Reynolds, 1971). Our study provides no justification for the discomfort and expense of this time-honoured custom.

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Procarbazine (Natulan) in the Treatment of Peyronie's Disease

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Summary—Thirty-four men with Peyronie's disease were treated with a 12-week course of the drug procarbazine (Natulan), preceded or followed by a 12-week course of vitamin E.

Ninety-one per cent of the men failed to improve or became worse whilst receiving Natulan and toxic side-effects were common. In comparison 39% improved whilst taking vitamin E.

We conclude that Natulan is of little benefit in the treatment of this condition and may indeed be harmful.

In the 16th century Andreas Vesalius wrote to his pupil Fallopius "A certain distinguished man who consulted you at Padua . . . had some nodules which twisted his penis quite remarkably so that it came to the shape of a ram's horn." Regrettably the treatment recommended by these celebrated medical men is not recorded, although the fact that a second opinion was sought suggests that Fallopius, at least, was unable to provide a cure.

It seems likely that their patient had Peyronie's disease. This title remains as a tribute to François de la Peyronie who, summoned to Paris from Montpellier by the Sun King, Louis XIV, eventually rose to become court surgeon to Louis XV and to be the founder of the Royal Academy of Surgery in Paris. In 1743 he described the condition which now bears his name in a paper entitled "Some observations opposing the normal ejaculation of semen" (Peyronie, 1743). The 3 cases which he reported all had fibrous thickening of the shaft of the penis (described as rosary beads) with resulting pain and curvature on erection. Peyronie believed the condition to be a sequel of venereal disease and after the eradication of the virus venerien (for which he used mercury) sent his patients to bathe in the waters of the fashionable spa town of Barèges, made popular by the patronage of Madame de Maintenon.

He reported a 100% cure rate, a degree of success which has never since been equalled.

A list of some of the more popular remedies (Table 1) serves by its length to emphasise our lack of understanding of this condition and how it should best be treated.

Table 1 Peyronie's Disease: Methods of Treatment

1. Physical Methods:
   - Massage
   - Hyperpyrexia
   - Ultrasonic vibration
   - Irradiation
2. Drugs:
   - Iodinated ointment
   - Potassium para-amino benzoate (Potaba)
   - Oestrogens
   - Dimethyl sulfoxide (DMSO)
   - Steroids
   - Vitamin E
   - Procarbazine (Natulan)
3. Operations

In 1968 Aron noticed that a patient being treated for Hodgkin's disease with the alkylating agent procarbazine developed an improvement in his Dupuytren's contractures. Aboulker and Benassayag (1970) reported encouraging results for the treatment of Peyronie's disease with this drug, 52% of their 17 patients being cured within 2 months of treatment and a further 24% being partially improved.

In view of this encouraging report it was decided to mount a simple clinical trial in which procarbazine would be compared with vitamin E as a treatment for Peyronie's disease.

Patients and Methods

Thirty-four patients who presented between January 1975 and May 1976 were included in the

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trial. None had received any previous treatment and young men, especially those who had not completed their families, were excluded due to the risk of testicular and chromosome damage by procarbazine (Chesney, 1975).

Thirty-two of the patients were white Europeans with 1 Indian and 1 Pakistani.

The age of the patients ranged from 21 years to 65 years with a mean of 49 years.

Table 2 Peyronie's Disease: Symptoms

Pain	20	(58%)
Lump	34	(100%)
Deformity	33	(97%)
Difficulty with intercourse	24	(70%)

Pain was a prominent symptom in 20 patients (Table 2) whilst all complained of a palpable lump and most of a deformity of the penis on erection; 75% had a deformity of more than 45°; 24 (70%) experienced difficulty with intercourse.

At the time of presentation symptoms had been present for from 1 month to 3 years with an average period of 15 months.

Penile calcification was found on X-ray in 5 of the patients (14.7%) whilst Dupuytren's contractures were recorded in 8 cases (23.5%).

After an initial visit, those patients with even registration numbers were commenced on a 12-week course of procarbazine 50 mg bd followed by tocopheryl acetate (Ephynal) 200 mg tds for 12 weeks, whilst those with odd numbers received the drugs in the reverse order.

While receiving procarbazine the patients were issued with monoamine oxidase inhibitor warning cards and underwent regular white blood cell counts.

Table 3 Peyronie's Disease: Assessment Scoring

Pain	Severe	2
	Moderate	1
	Nil	0
Deformity	>45°	2
	<45°	1
	Nil	0
Lump	Well defined	2
	Ill defined	1
	Absent	0
Penetration	Impossible	2
	Difficult	1
	Easy	0
Erection	Strong	2
	Weak	1
	Nil	0
Intercourse	Impossible	2
	Difficult	1
	Satisfactory	0

The patients were seen at monthly intervals by 1 clinician (JPP) when symptoms were assessed and the penis examined for the size of plaque.

In order to assist in the accurate monitoring of their progress, a simple scoring system was instituted (Table 3). Each symptom and sign was scored retrospectively by another observer from 0 to 2 depending on its severity and at the end of 3 months of treatment with each drug the scores were added and compared with the baseline score total at presentation. A total score after treatment that was in excess of a corresponding presentation score by 2 or more was taken as indicative of improvement.

Results

Of 31 men treated with procarbazine only 22 (65%) completed a full 12-week course of treatment (Table 4). Two improved whilst 19 showed no improvement and 1 actually became worse while taking the drug. Thus only 9.1% improved and 90.9% either remained static or became worse.

Table 4 Peyronie's Disease: Response to Procarbazine Treatment

Cured	0	9.1%
Improved	2	
Not improved	19	90.9%
Worse	1	
Total	22	100%

Thirty-three men received treatment with vitamin E and of these 31 (91%) completed a full course of the drug. At the finish of treatment 2 patients were considered cured and 10 improved (Table 5). Nineteen showed no signs of improvement. Therefore a significantly greater number of patients improved on vitamin E ($x^2 = 5.8067$, $p < 0.02$).

Table 5 Peyronie's Disease: Response to Vitamin E Treatment

Cured	2	38.7%
Improved	10	
Not improved	19	61.3%
Worse	0	
Total	31	100%

Generally vitamin E was well tolerated and gave rise to no unpleasant side effects, although 2 of the 33 men given this drug defaulted before completing the 3 months of therapy.

Troublesome side-effects were common in those receiving procarbazine. These consisted of gastrointestinal disturbances (6 patients), severe headaches (2 patients), skin eruptions (2) and a leucopenia. To this list one must add alcohol intolerance and many patients had to curb their intake of alcohol.

In 6, the side-effects were sufficiently severe for the drug to be discontinued and a further 3 patients defaulted before completing a full course of treatment with procarbazine. No improvement of the Peyronie's disease was noted in any of these patients.

Discussion

This trial has shown that procarbazine has little to offer in the treatment of Peyronie's disease and this is in keeping with the findings of Oosterlinck and Renders (1975).

The question now arises whether vitamin E has any merits as an effective form of treatment as was first suggested by Scardino *et al.* (1949).

The natural history of Peyronie's disease is one of slow improvement and Williams and Thomas (1970) found that 9 out of 12 untreated patients improved in periods ranging from 15 months to 8 years (with an average of 4 years).

The finding that 39% of patients improved within 12 weeks while taking vitamin E suggests that it is worth performing a proper double blind controlled trial to assess the efficacy of this drug.

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Surgical Management of Impotence using the Inflatable Penile Prosthesis: Experience with 103 Patients

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Summary—The inflatable hydraulic penile prosthesis has been implanted in 103 patients with both organic and psychogenic impotence.

The 4 failures in this series resulted from infection. Mechanical problems occurred in 27 patients, but with additional implant experience, these have been significantly reduced. All mechanical complications are correctable through secondary and tertiary surgical procedures. Ninety-eight of 99 patients with a normally functioning prosthetic device had satisfactory intercourse without significant difficulty.

The inflatable penile prosthesis has proved to be a highly satisfactory method of treating male impotence.

The surgical management of organic impotence received little attention until 1964, when Lash *et al.* (1964) described the use of a silicone inlay for plastic reconstruction of the penis after surgical treatment for Peyronie's disease. Pearman (1967) then applied the concepts as described by Lash *et al.*, devising a silicone rod that could be implanted between Buck's fascia and the tunica albuginea and that was effective enough to permit vaginal penetration without buckling of the penile shaft. The use of this device has been satisfactory in the treatment of the organically impotent male. The size and shape of the silastic rod have been improved to conform to the variability in penile size and to permit ease of insertion. Pain with intercourse generally has not been a problem; however, migration of the rod has occurred, and this occasionally has led to painful intercourse and buckling of the glans penis.

Recently, the availability of this device has been restricted as the result of reports indicating that, in at least 1 patient, breakage occurred, resulting in buckling of the shaft as well as pain and requiring removal (Mandler, personal communication).

In 1973, Scott *et al.*, reported their initial experience with the inflatable penile prosthesis, a totally implantable device using inflatable silastic cylinders placed inside each corpus cavernosum and connected by silastic tubing to a pumping mechanism implanted in the scrotal pouch; the fluid for inflation is provided by a reservoir implanted behind the rectus muscle.

Small and Carrion (1975) reported the development and use of a silastic prosthesis which consisted of 2 semirigid moulded silicone rods implanted side by side in the matrix of each corpus cavernosum. The technique, results, advantages, and disadvantages of the device have been previously reported (Furlow, 1976).

Until about 2 years ago, urologists at the Mayo Clinic managed the organically impotent male by implanting the Pearman prosthesis. At that time, however, our favourable experience with the inflatable genitourinary sphincter in treating male incontinence led us to consider using the Scott prosthesis for the treatment of organic impotence.

This report summarises our experience with the inflatable penile prosthesis in 103 patients with impotence who were seen during the period October 1974 to December 1976.

Patients and Procedure

Patient Selection. In our series, impotence was presumed to follow as a recognised complication of certain disease states in 103 patients (Table 1).

To establish the organic basis for the impotence in a clinical setting, we relied on the history, the MMPI (Minnesota Multiphasic Personality Inventory)

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Table 1 Causes of Impotence in 103 Patients with Inflatable Penile Prosthesis

Cause	*Number of patients*
Postperineal trauma	13
Postprostatectomy	17
Postcystectomy	5
Neurologic disorders	11
Diabetes	25
Psychogenic	10
Physiological	8
Peyronie's disease	5
Proctocolectomy	2
Postradiation	1
Estrogen therapy	1
Peripheral vascular disease	2
Coronary artery disease	3
Total	103

psychological consultation, and lengthy discussion with the patient, his spouse, or in some instances with the patient's fiancée—in the last instance, with the permission of the patient and in his presence. Early in our experience, we excluded as surgical candidates those patients with functional or psychogenic impotence; however, we now recognise that some patients with psychogenic impotence should be seriously considered as suitable candidates for implantation. Of the 103 patients, 10 with functional or psychogenic impotence have undergone implantation of the inflatable penile prosthesis.

In addition, the clinician must be certain of the patient's motivation to undergo implantation. To this end, an important feature of the interview has been the description and demonstration of the prosthetic device, including its advantages and the potential complications and risk involved. To aid in this discussion, we use a model with the prosthesis in place.

Age Distribution. The youngest patient in our series was a 22-year-old man with an imperforate anus, neurogenic dysfunction of the bladder, and lifelong impotence. The oldest man in our series was 77 years of age (Table 2). In the absence of chronic or debilitating disease state, age alone should not be a factor in patient selection.

Table 2 Age Distribution of 103 Patients with Inflatable Penile Prosthesis

Age (years)	*Number of patients*
20-29	12
30-39	10
40-49	22
50-59	27
60-69	28
70-79	4
Total	103

Surgical Considerations. As with any relatively new surgical technique, the principles of successful implantation evolve as the result of experience with the procedure. The basic technique of implantation of the inflatable penile prosthesis has been described by Scott *et al.* (1973). As our experience has increased, we continue to modify the basic technique in an effort to minimise the potential complications (Furlow, 1976). Some of the specific surgical guidelines are summarised in Table 3.

Table 3 Surgical Recommendations for Implantation of Inflatable Penile Prosthesis

Incise tunica, incisions 1 to 1.5 cm dorsolaterally
Close tunica with 2-0 proline interrupted sutures
Dilate corpus with No. 10 Hegar dilator (avoid overdilatation)
Use cylinder size of approximately 0.5 cm less than measured
Place distal end of cylinder in glans
Place proximal end in deep subpubic portion of corpora
Avoid stretching penis when estimating size
Insert cylinder by instrument or freezing
Avoid overdistention of cylinder before and after insertion
Keep tubing in tissue planes with gentle curves
Make all connections distal to external ring in subcutaneous tissue
Place pump low in scrotum—outside the tunica vaginalis
Place reservoir posterior to rectus and anterior to posterior sheath
Test mechanism to ensure function after each layer of closure
Use small-calibre urethral catheter (12 F)

Modified from Furlow, W. L. (1976). Surgical management of impotence using the inflatable penile prosthesis: experience with 36 patients. *Mayo Clinic Proceedings*, **51**, 325-328.

Results

Complications occurred in 33 patients. The complications with this surgical procedure can be divided into 2 types: pathological and mechanical.

Pathological complications include infection of the prosthesis (4 patients), scrotal haematoma (3 patients), scrotal erosion (1 patient), and pump malposition (1 patient). The 2 problems with postoperative phimosis occurred early in the series. The most serious complication has been infection of the prosthesis, because it always necessitates total removal of the prosthesis in order to permit clearing of the infection. Fortunately, the incidence of infection in our series was low (4 of 103 patients).

Mechanical problems with the device occurred in 27 patients (Table 4). A number of these problems can be avoided through strict adherence to specific surgical guidelines as outlined in Table 3.

In a recent survey of our results after 1 year, and again after 2 years of experience with implantation,

Table 4 Mechanical Complications in 27 Patients with Inflatable Penile Prosthesis

Complication	*Number of patients*	*Disposition*
Cylinder buckling	5	Replaced
Cylinder ballooning	9	Replaced
Cylinder rupture	1	Replaced
Cylinder leak	2	Replaced
Inadequate cylinder length	2	Replaced
Tubing kink	4	Corrected
Fluid loss	6	New prosthesis
Pump defect	1	Replaced
Total	30*	

* 3 patients had 2 mechanical complications each.

we found a reduction of 17% in mechanical complications—from 25% during the first 14 months to 8% during the past 12 months (5 of 60 patients). Fortunately, these mechanical problems were all correctable, though requiring secondary and tertiary surgical procedures.

The results of implantation with the inflatable penile prosthesis have been satisfactory. Of the 103 patients, 99 have normally functioning prostheses. The 4 failures resulted from infection involving some portion of the prosthetic device. In each instance, the entire device was removed in order to clear up the infection.

Of the 99 patients with a normally functioning prosthesis, 98 have reported that satisfactory intercourse has been achieved without significant difficulty. One patient continues to find it difficult to insert the penis when the device is inflated, and he plans to return shortly for evaluation. Buckling of the glans penis may occur as the result of malpositioning of the prosthesis within the corpora at the distal end beneath the glans.

Discussion

The inflatable penile prosthesis, thus far, has proved to be a highly satisfactory method of treating organic impotence. Our experience was originally limited to patients considered to have organic impotence. During the past 6 months, we have enlarged our guidelines for patient selection to include those with functional or psychogenic impotence who are considered to be emotionally unstable for implantation of the penile prosthesis. Through careful patient screening and the cooperative efforts of a clinical psychologist or a psychiatrist interested in the problems of human sexual behaviour, we have avoided implanting the device in patients who, because of deep-seated emotional problems, would not benefit from implantation. This is often a difficult decision when such emotional problems exist in an organically impotent male, because implantation may improve the patient's emotional state. We believe that use of the MMPI, as well as psychiatric consultation, is essential for valid patient care in achieving the goals implied in the use of penile prosthetic devices. The use of this device in the psychologically impotent male requires these stringent guidelines in patient selection. From the urologists' viewpoint, we must be prepared to handle the possible consequences resulting from the strong dependence on the physician that occurs as the result of surgical implantation of a mechanical device in an emotionally unstable patient. Transfer of this dependence from psychiatrist to urologist, if it occurs, can be premature, which is unsettling for both physician and patient.

The patient-partner acceptance has been excellent. Orgasmic sensation is preserved, and when present before the onset of impotence, ejaculation is unaffected. Pain has not been a problem after the first 6 weeks unless associated with 1 of the complications mentioned. Long-standing low-grade pain that moves from 1 portion of the prosthesis to another should cause the physician to suspect an infection within the spaces surrounding the silastic material. Experience with the genitourinary sphincter indicates that infection of this kind may be present for months, causing only low-grade pain until it becomes evident clinically by reaching the skin surface in a dependent portion of the prosthesis—either in the scrotal pouch or in the distal end of the corpus cavernosum.

The mechanical problems initially encountered have been significantly minimised as further experience is gained with the surgical technique. The mechanical problems associated with this device are easily recognised if the physician understands how the device functions. The 25% Hypaque solution that is used to fill the system permits good roentgenographic visualisation of the device. It is important to take films with the device both inflated and deflated. In our experience, mechanical problems have been correctable but only by surgical intervention. The reasons for some of these complications remain unclear. Material defects occasionally have been recognised, and new production methods are under investigation by the manufacturer. However, most of the major mechanical problems in our series probably can

Table 5 Post-operative Considerations after Implantation of Inflatable Penile Prosthesis

Partially inflate prosthesis for 7 to 10 days
Avoid asymmetric dilatation of cylinders
Inflate and deflate mechanism daily
Position pump daily to avoid kinking
Remove catheter early—third or fourth day post-operatively
Instruct patient in use of pump—use sample prosthesis to demonstrate
Instruct patient to avoid early active usage for 4 to 6 weeks
Instruct patient in initial usage

Modified from Furlow, W. L. (1976). Surgical management of impotence using the inflatable penile prosthesis: experience with 36 patients. *Mayo Clinic Proceedings,* **51**, 325-328.

be prevented by strict adherence to the surgical principles listed in Table 3. In addition, the post-operative care should follow certain specific guidelines (Table 5) to ensure further the functional success of the procedure.

Our experience indicates that implantation of the inflatable penile prosthesis is a highly acceptable method of treating organic impotence.

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The Thermographic Characteristics of Varicocele: an Analysis of 65 Positive Registrations

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Summary—Sixty-five positive thermograms in patients suspected of subclinical varicocele or presenting with clinically palpable varicocele have been analysed. Two distinct patterns of varicocele associated thermograms could be distinguished, hyperthermia always exceeding 1 °C.

A correlation was found between the clinical grade of varicocele and both the extension and the degree of hyperthermia.

The value of scrotal thermography in the diagnosis of varicocele is now being accepted by most andrologists and urologists. The present study concerns 118 thermograms performed in 110 patients, all consulting 1 of us (F.C.) for infertility, associated with sexual impotence, combined with varicocele. The thermographic diagnosis was found to be correct in 111 out of 118 thermograms (93%) (Comhaire *et al.*, 1976).

In 65 out of the 110 patients the presence of reflux was certified by clinical examination and, if required, by selective retrograde venography (Comhaire and Kunnen, 1976).

Methods

We use an infrared camera AGA thermovision unit No. 680. The examination is performed in a room kept at constant temperature between 20 and 22°C. The distance between the camera and the patient is 0.90 m. Both conventional thermograms and isotherm recordings are made, with a temperature discrimination of 0.5°C, and only anterior views are taken. The pictures are recorded on polaroid films. The patient stands upright with his legs spread. The penis is fixed on the abdominal wall with a bandage and the scrotum is separated from the thighs by interposition of another bandage. By doing so, we can make a distinction between the heat caused by the scrotum and that caused by the thighs. Recordings are performed after an adaptation time of 15 min. The results of the clinical examination are noted according to the staging by Dublin and Amelar (1970), to which the stage of subclinical varicocele is added.

Subclinical varicocele: reflux is present in the spermatic vein, however, no distension of the pampiniform plexus can be palpated.

Grade I:	Small varicocele: the mass of veins is less than 1 cm in diameter. The reflux during Valsalva manoeuvre can be detected.
Grade II:	Moderate varicocele: on palpation during Valsalva manoeuvre, the bulk of veins is estimated to have a thickness of 1 to 2 cm.
Grade III:	Large varicocele: on palpation the bulk of venous channels is greater than 2 cm in diameter on Valsalva manoeuvre.

Results

A. Thermogram of the normal scrotum (Fig. 1). The normal scrotum gives a completely symmetrical picture with the following characteristics (Kormano *et al.*, 1970):

(1) The scrotal skin is cooler than that of the medial aspect of the upper thigh, the temperature difference being more than 3°C.
(2) The central, cranial part of the scrotum is warmer than the lateral sides.
(3) The penile shaft is relatively cold; its skin, however, is warmer than the scrotal skin.

B. The varicocele is thermographically characterised by the presence of an area with increased temperature (Gasser *et al.*, 1973).

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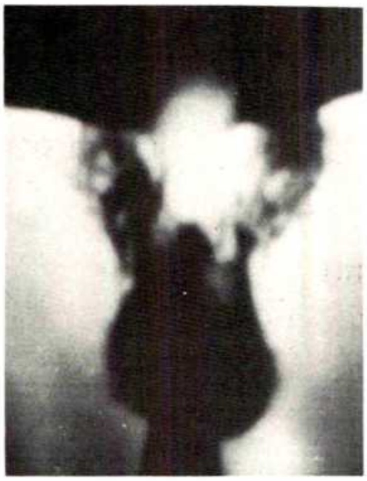

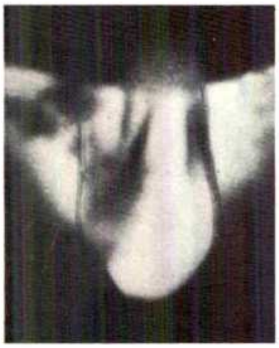

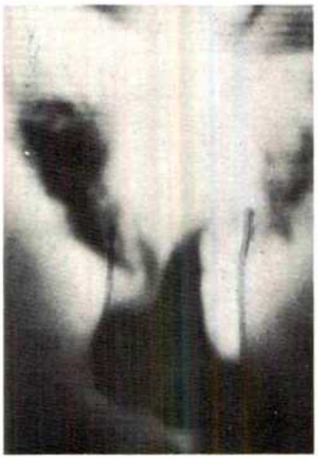

Fig. 1 Normal scrotal thermogram: symmetrical picture of the scrotum.

Fig. 2 Varicocele-associated thermogram: Type A, hyperthermia of the entire left hemiscrotum.

Fig. 3 Varicocele-associated thermogram: Type B, hyperthermia, limited to the upper part of the left side of the scrotum.

(1) Localisation and extension of the hyperthermic area. According to the hyperthermic pattern, essentially 2 different types can be distinguished (Figs. 2 and 3): hyperthermia of the entire hemiscrotum (Type A), and hyperthermia limited to the upper part of the affected hemiscrotum (Type B).

In our series of 65 positive thermograms Type A was found in 30 and Type B in 32 cases. In 3 patients the whole scrotum was warmer than normal, 2 of these presented with bilateral varicocele, the third had a unilateral left varicocele Grade III.

A good correlation is found between the extension of the hyperthermic area and the clinical stage (Table 1). Indeed, 22 out of 31 (71%) patients with subclinical and Grade I varicocele presented a Type B pattern, whereas in Grades II and III patients hyperthermia was of Type A in 21 out of 31 cases (67%).

(2) Degree of temperature increase associated with varicocele. Varicocele-induced increase in temperature can be appreciated by comparing the affected with the contralateral side of the scrotum. The 3 cases presenting hyperthermia of the entire scrotum are excluded from this part of the study.

Table 1 Correlation between Clinical Grade and Thermographic Pattern

Clinical grade	*No.*	*Thermographic type*	
		A	*B*
Subclinical and Grade I varicocele	31	9	22
Grades II and III varicocele	31	21	10
Total	62	30	32

Table 2 Temperature Increase caused by Varicocele

Increase (degrees C)	0.5	1	1.5	2	2.5	3 or >3	
No.	0	7	9	8	8	30	62 (total)

Table 2 shows that a difference of 1°C or more suggests the diagnosis of varicocele, a smaller temperature difference being, in our experience, easily induced by other factors such as skin folds.

Furthermore our data indicate the existence of a correlation between the clinical grade and the degree of temperature difference (Table 3). Indeed, only 10 out of 31 (32%) subclinical or Grade I varicoceles display a temperature difference of 3°C or more as against 20 out of 31 (64%) Grade II and III cases with hyperthermia of 3°C or more.

(3) Special attention was given to the analysis of

Table 3 Correlation between Clinical Grade and Difference in Temperature

Clinical grade	*No.*	⩽2.5°C	⩾3°C
Subclinical and Grade I varicocele	31	21	10
Grades II and III varicocele	31	11	20
Total	62	32	30

Table 4 Post-operative Thermograms

Number of patients	*Temperature of the operated side*
11	Higher: 5 patients: 2°C 2 patients: 2.5°C 4 patients: 3°C (1 false positive)
27	Equal
5	Lower: 3 patients: 0.5°C 2 patients: 1°C
2	Lower: 1 patient: 2.5°C 1 patient: 3°C

45 additional post-operative thermograms (Table 4). It is known that, after operation, the temperature of the affected side may be lower than that of the contralateral hemiscrotum (Kormano *et al.*, 1970). In 11 patients the post-operative thermogram showed a persistent hyperthermia of the operated side; 10 of these cases presented spermatic venous reflux on the retrograde venogram whereas in 1 patient reflux was found to be completely interrupted.

In 32 patients the scrotal temperature of the operated side was either equal to (27 cases) or lower than (5 cases) that of the contralateral hemiscrotum. Temperature difference in these last cases never exceeded 1°C.

Two patients presented a strongly hyperthermic spot at the right hemiscrotum after ligature of the left spermatic vein. In them reflux was shown to be present in the right spermatic vein, proving that they had suffered from undetected bilateral varicocele.

Discussion

In 93% of our cases with palpable and non-palpable varicocele the diagnosis was accurately made by thermography. The characteristics of 4 false positive thermograms, obtained in patients in whom other investigations did not confirm the existence of spermatic venous reflux, are summarised in Table 5.

Three of these false positive cases showed a Type B picture with a temperature difference of 1°C. The fourth recording was of Type A with a temperature increase of 1.5°C. In 3 of the 4 patients the false positive recording could tentatively be related to orchido-epididymitis in 1 case and recent surgery for inguinal hernia in 2 cases.

Table 5 Thermographic Characteristics of 4 False Positive Thermograms

	Pattern	*Increase of temperature*
Case 1	A	1.5°C
Case 2	B	1°C
Case 3	B	1°C
Case 4	B	1°C

In 3 patients false negative thermograms were obtained (Table 6).

Table 6 Characteristics of 3 False Negative Thermograms

	Clinical grade	*Retrograde phlebography*
Case 1	Grade II	Positive
Case 2	Grade III	Positive
Case 3	Subclinical	Positive

Two of these had clinically palpable varicocele, but presented simultaneously with homolateral testicular atrophy, due to torsion in 1 and to operation for inguinal hernia in the other case. The third patient had a positive retrograde phlebogram, whereas clinical examination was inconclusive. We have no explanation for the lack of thermographic response in this case.

It would appear from our data that the simple and innocuous technique of scrotal thermography deserves a place as a reliable screening method for varicocele in patients with male infertility.

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Adenomatoid Tumour of the Epididymis: Histochemical and Ultrastructural Study of 2 Cases

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Summary—Two cases of adenomatoid tumour of the epididymis are described. Both the histochemical and ultrastructural studies support the concept that it is of mesothelial origin.

The histochemical study showed the presence of acid mucopolysaccharides in the lumen of the tubular structures.

The epithelial cells presented numerous microvilli in the free surface, junction complexes, wide intercellular channels and a well-developed Golgi complex.

Abundant bundles of microfilaments and intracellular spaces were observed in the cytoplasm.

Lymphocytes and histiocytes were identified both in the tubular lumen and between the epithelial cells.

The stroma of the tumour was made up of dense connective tissue with abundant bundles of elastic fibres.

The presence of intracytoplasmic spaces in the epithelial cells and elastic fibres in the stroma had not been previously observed in this tumour.

The adenomatoid tumour is the most frequent tumour of the epididymis (Broth *et al.*, 1968). It has also been observed in the tunica vaginalis (Evans, 1943; Ambrose, 1953; Malament and Ries, 1964; Miller and Lieberman, 1968) and in the spermatic cord (Mostofi and Price, 1973). In females, it has been described on the surface of the ovary (Jackson, 1958; Teel, 1958), in the fallopian tube (Evans, 1943; Fajers, 1949) and in the broad ligament (Akhtar *et al.*, 1976).

The adenomatoid tumour of the epididymis appears as an ovoid structure, small in size, solid, well differentiated from the testis, and affecting mainly adults.

The histogenesis of the tumour has led to great controversy. It has been considered to have either an endothelial, mesonephric (Teilum, 1954), Mullerian (Sundarasivarao, 1953) or mesothelial (Masson *et al.*, 1942) origin. The latter hypothesis has been recently reinforced with the results of histochemical and ultrastructural studies (Marcus and Lynn, 1970; Mackay *et al.*, 1971).

We present in this paper the optical, histochemical and ultrastructural study of 2 adenomatoid tumours of the epididymis which showed several characteristics not previously reported.

Case Reports

Case 1. A 46-year-old patient complained of progressive enlargement of the right scrotum. A nodule was found in the head of the epididymis and excised. Its longest diameter measured 2.5 cm.

Case 2. A 51-year-old patient had been thought to have epididymitis on the left side. His epididymis appeared thick and painful. An epididymectomy was performed and a solid tumour, 3 cm in diameter, was found in the head of the epididymis.

Material and Methods

Specimens from both tumours were fixed in formalin and embedded in paraffin. They were studied with Haematoxylin and Eosin (H & E), Alcian blue at low pH, Periodic acid-Schiff (PAS), Masson trichrome and Van Gieson elastic techniques.

Small blocks of tissues were fixed in cacodylate-buffered gluteraldehyde and postfixed in 1% phosphate-buffered osmium tetroxide for 2 h, dehydrated

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and embedded in Epon 812. Sections of 1 micron thickness were stained with toluidine blue. The ultrathin sections were double stained with uranyl acetate and lead citrate and were subsequently studied in a Philips 300 electron microscope.

Results

In the sections observed under a light microscope the appearances of the tumours were similar in both cases. They consisted of tubular structures of variable diameter, lined by cuboidal or flat cells (Fig. 1). Intercellular channels of varying size were seen between the epithelial cells. Intracytoplasmic spaces were present in some of these cells. Another cell type, with round or folded nucleus and clear or vacuolated cytoplasm was observed between these epithelial cells as well as in the lumen of the tubular structures (Fig. 2). The stroma was fibrous, dense, with abundant collagen fibres, thick elastic fibres and lymphocytes (Fig. 3). Abundant acid mucopolysaccharides were identified in the tubular lumina with Alcian blue stain.

The electron microscope study revealed the following findings. The size and shape of the cells lining the tubular structures varied widely. A basement membrane outlined the tubules. The luminal face of the epithelial cells showed numerous and fine microvilli. Junction complexes (Fig. 4) and intercellular channels between the cells were detected (Fig. 5). These latter were present at different levels and had irregular lumina with a variable number of microvilli protruding into them (Fig. 5). The cytoplasm of the epithelial cells contained irregularly scattered small cisternae of granular endoplasmic reticulum, a well developed Golgi complex (Fig. 6), numerous bundles of microfilaments and mitochondria. Some of these cells showed intracytoplasmic spaces with microvilli in them (Fig. 4).

Active fibroblasts, surrounded by bundles of collagen and elastic fibres, some mast cells, lymphocytes and histiocytes were observed in the interstitial tissue.

The cells present in the tubular lumina and in the intercellular channels of the epithelium were identified as histiocytes and lymphocytes.

Discussion

The adenomatoid tumour is a peculiar variety of benign mesothelioma. The epithelial component consists mainly of tubules of irregular shape. The rest of the tumour is composed of connective tissue, sometimes loose, sometimes fibrous.

The cells lining the different tubular structures have many properties in common with mesothelial cells (Hesseldahl and Larsen, 1969). The presence of abundant microvilli in the tubular lumen, junction complexes, enlargement of the intercellular spaces and bundles of microfilaments in the cytoplasm are ulstrastructural features observed in the human mesothelium (Hesseldahl and Larsen, 1969). These observations, together with the presence of acid mucopolysaccharides in the tubular lumina, reinforce the hypothesis of the mesothelial histogenesis of these tumours (Marcus and Lynn, 1970; Mackay *et al.*, 1971; Ferenczy *et al.*, 1972; Taxy *et al.*, 1974).

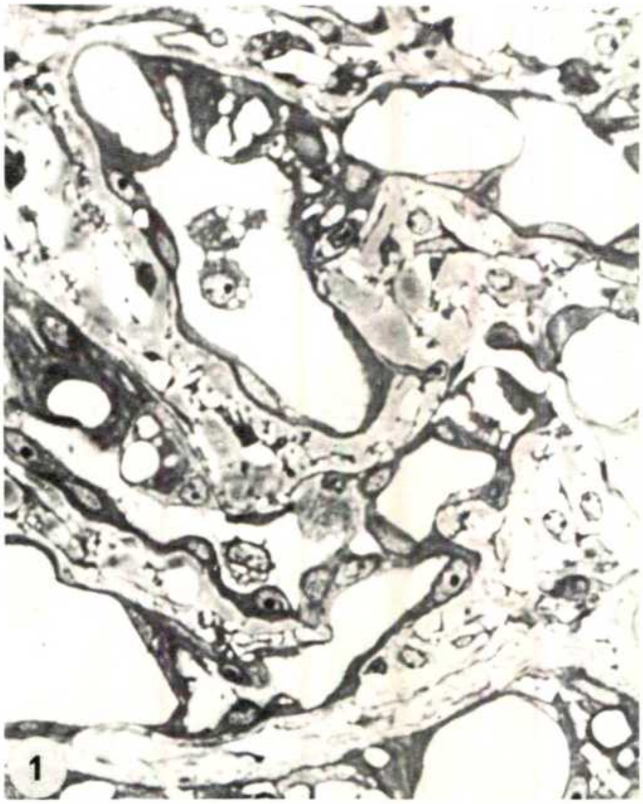
Our histochemical and ultrastructural findings confirm fully this hypothesis. On the other hand, we have observed ultrastructural and histochemical features of interest not previously reported.

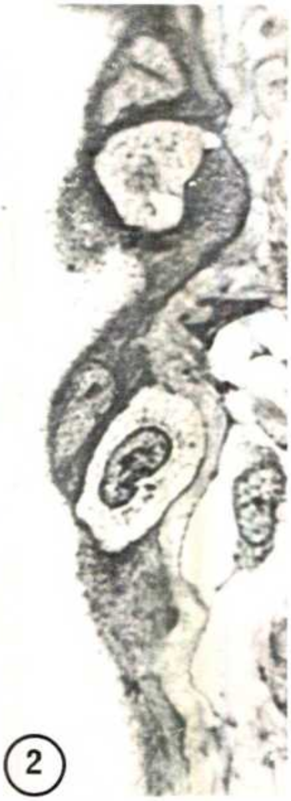
The epithelial cells showed a well-developed Golgi complex and secretory vesicles in direct relation with them. These vesicles probably contain the acid mucopolysaccharides detected in the tubular lumina with histochemical techniques.

Another interesting finding is the existence of microvilli in intracytoplasmic spaces in the epithelial cells. This fact, not hitherto described in adenomatoid tumours, has been observed in pleural malignant mesothelial tumours (Suzuki *et al.*, 1976). These intracytoplasmic spaces would be in close relation with the secretory activities of these cells.

The cells present in the intercellular channels and in the tubular lumen are histiocytes and lymphocytes. The more severe degeneration in the cells lodged in the tubular lumen suggests the existence of a migratory process from the stroma to the lumen through the intercellular channels. A similar migration of cells has been observed in the glandular epithelium of the human endometrium (Vázquez and Domínguez, 1974) and in the intestinal epithelium (Toner and Ferguson, 1971).

The stroma of the adenomatoid tumour has been described as made up of fibroblasts, collagen fibres, blood vessels and some mast cells (Mostofi and Price, 1973). The presence of abundant elastic fibres was significant in our cases. This fact had only been previously observed in an adenomatoid tumour of the broad ligament (Akhtar *et al.*, 1976), but is frequent in breast cancers (Lundmark,





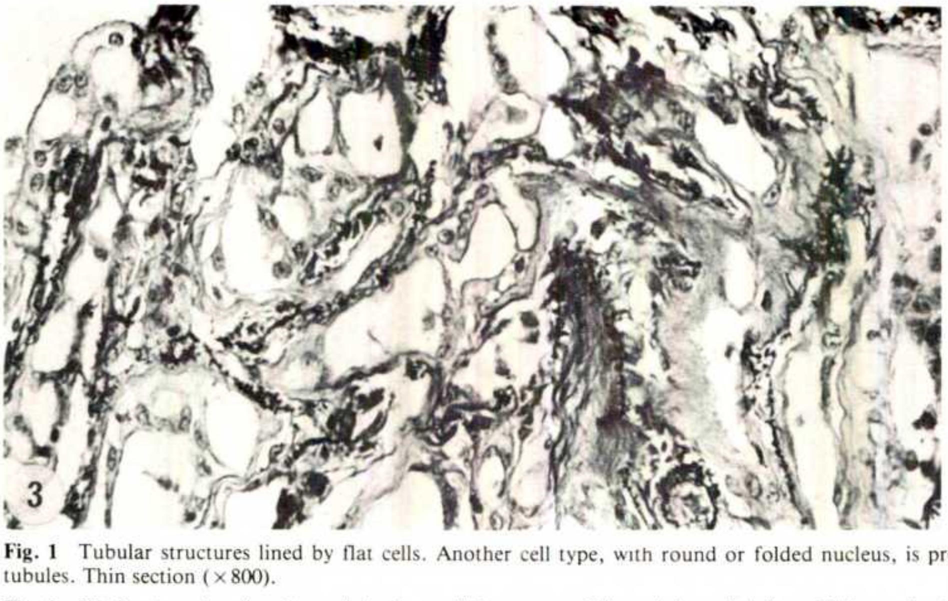
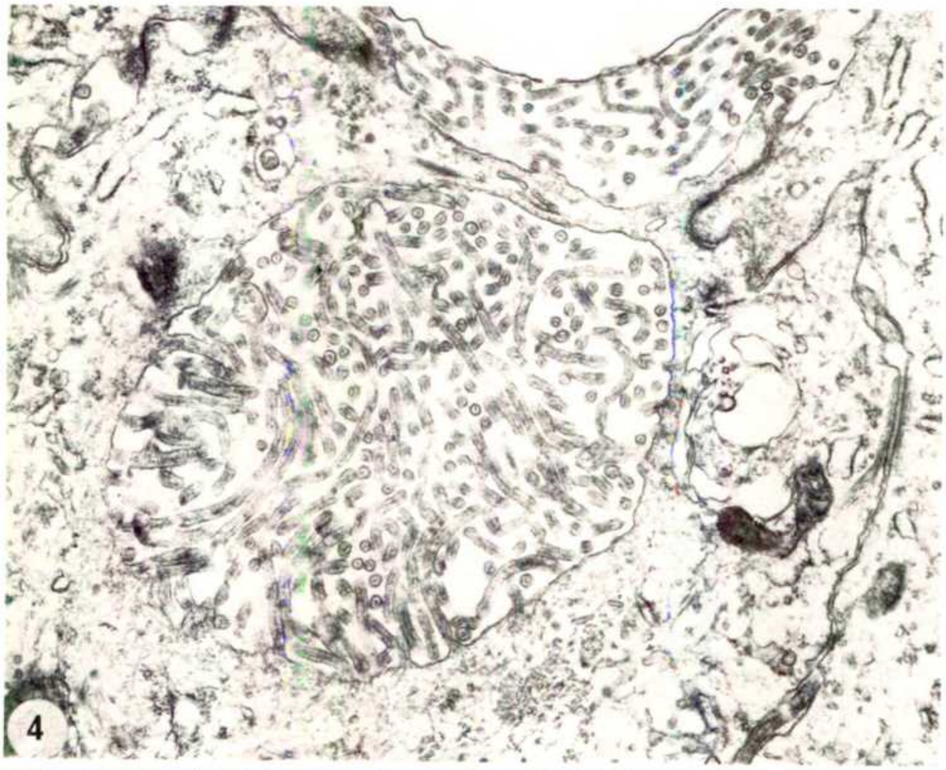
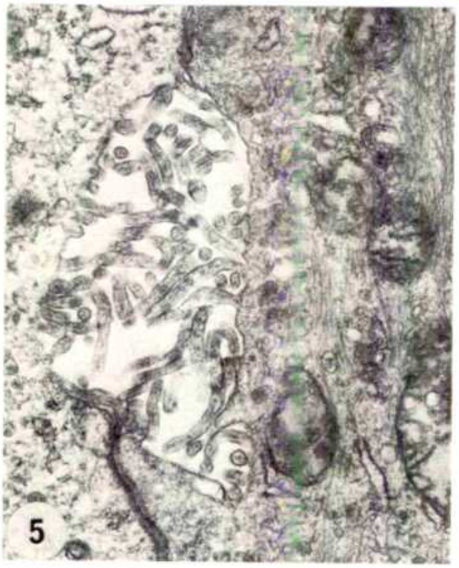


Fig. 1 Tubular structures lined by flat cells. Another cell type, with round or folded nucleus, is present in the lumen of the tubules. Thin section (× 800).

Fig. 2 Histiocytes migrating through the intercellular spaces of the tubular epithelium. Thin section (× 2000).

Fig. 3 Tumour stroma showing abundant elastic fibres (black) and bundles of collagen fibres (grey). Van Gieson elastic (× 400).





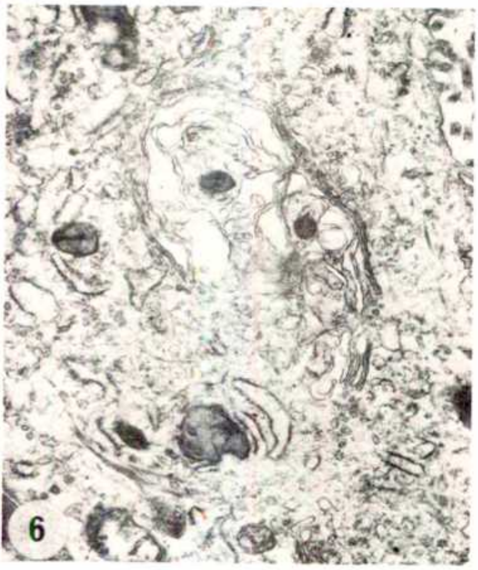


Fig. 4 Luminal face of 3 epithelial cells showing junction complexes. The central cell presents an intracytoplasmic space with a great number of microvilli (× 23,200).

Fig. 5 Intercellular channel with microvilli between 2 epithelial cells. Bundles of microfilaments can be seen in the cytoplasm of these cells (× 29,000).

Fig. 6 Secretory vesicles within the developed Golgi complex in an epithelial cell. Some cisternae of granular endoplastic reticulum are present in its neighbourhood (× 15,000).

1972). The mechanism by which certain types of epithelium induce the appearance of a fibroelastic stroma is as yet unknown.

At the present time, although there is good evidence of a mesothelial origin of the adenomatoid tumour, there is increasing support for the use of the alternative term "benign mesothelioma of the genital tract" as suggested by Masson *et al.* (1942). However, we feel that the designation "adenomatoid tumour" should be kept, as being more descriptive.

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Chyluria—a 10-Year Follow-up

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Summary—One hundred and sixty-one cases of chyluria have been studied.

The possible aetiological factors, the approach to investigation and the methods and results of treatment have been discussed.

In this series, the diagnosis was established by the presence of chyle in the urine. Lymphography was carried out in 90 patients for the localisation of the site of lymphatic reflux while cystoscopic examination after fatty meal was useful in determining the side with the heavier leakage.

One hundred and nineteen cases responded to conservative treatment and only 42 cases required operative treatment.

Stripping of the renal pedicle via the retroperitoneal route gave the best results.

Chyluria—the presence of chyle in urine—is an interesting phenomenon with dramatic and alarming presentation. Surprisingly enough, the disease is not rare in this part of the world (Ray and Rao, 1939; Akisada and Tani, 1968; Chang *et al.*, 1973). Though not a life-threatening disease, its occurrence is usually extremely disturbing to the sufferer's morale, may occasionally even be debilitating due to the loss of absorbed food nutrient and in severe cases may produce urinary tract obstruction from chylous clots formation (Taylor *et al.*, 1975).

Herein we report our 10-year experience of this pathological entity, with emphasis on the clinical presentation, diagnostic criteria, possible aetiology and the methods and results of treatment.

Patients and Methods

A total of 161 patients with chyluria were seen from 1962-75 in the Genito-urinary Service of the Department of Surgery, University of Hong Kong.

There were 81 males and 80 females, giving an equal sex distribution. The youngest age of onset of symptoms was 9 years and the oldest 75 years.

Symptomatology

A detailed analysis of the symptomatology is seen in Table 1. The length of history of chyluria varies from as short as 2 weeks to as long as 30 years before the patient seeks medical advice.

Table 1 Symptomatology

Chyluria	161
Chylous clots	74 (46%)
Chylous clot retention	9 (5.5%)
Haematuria	37 (23%)
Loin pain	13 (8%)
Dysuria	68 (42%)
Weight loss	63 (39%)

The presence of "milky" urine usually aggravated by a heavy meal is invariably present, besides which 74 cases (46%) gave a history of clot colic while 9 (5.8%) developed chylous clot retention of urine. The "milky" urine may occasionally be associated with blood (haematochyluria) and this occurred in 37 cases (23%); 2 of these were found to have renal tuberculosis and 1 urothelial tumour of the renal pelvis at subsequent investigation. Loin pain occurred in 13 (8%) of the patients while 68 (42%) complained of dysuria. Weight loss occurred in 63 (39%) of all the patients studied.

Associated Diseases (Table 2)

In an attempt to elucidate the possible aetiological factors, detailed analyses were made of any associated diseases of these 161 patients. Twelve patients

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Table 2 Associated Conditions

Urological:	
Tuberculosis	5
Hydrocoele	5
Carcinoma of renal pelvis	1
Ureteric stone	1
Others:	
Pulmonary tuberculosis	7
Inguinal hernia	1
Pyogenic spondylitis	1
Fractured spine	1

were found to have other associated urological lesions; 5 renal tuberculosis, 1 urothelial tumour of the renal pelvis, 5 vaginal hydrocoeles and 1 ureteric stone. Ten patients had other possible significant diseases; of these 7 patients had a past history of pulmonary tuberculosis, 1 patient had had an inguinal hernia repaired, 1 had a history of pyogenic spondylitis and 1 a history of fractured spine. None of the patients exhibited features of elephantiasis although a history suggestive of filarial infection was present in 2 patients.

Diagnosis

All cases of suspected chyluria were investigated along 4 lines:

1. Confirmation of diagnosis

The finding of lymphocytes and the presence of fat globules in the urine (extracted with ether and stained red with Sudan III) formed the basic diagnostic criteria (Koo and Langenberg, 1969). The absence of such findings in a single random sample of urine, however, does not rule out the disease in patients with a history of "milky" urine. Further examination for fat globules in urine should be made, especially after a fatty meal. In this series, 108 cases showed evidence of chyle in the urine in the first random sample. Forty-five cases showed chyle only after repeated examinations following fatty food. In 8 cases no chyle was demonstrated in spite of repeated examination although the history of "milky" urine was unmistakable. Subsequent lymphographic studies, however, demonstrated the presence of lymphatico-calyceal fistulisation.

2. Localisation of the Site of Lymphatic Reflux and Fistulisation

(*a*) Cystoscopic Examination after a "fatty" Meal (Table 3)

Table 3 Results of 95 Cystoscopic Examination after a Fatty Meal

Bilateral chylous efflux	13
Unilateral chylous efflux, right	14
Unilateral chylous efflux, left	28
Negative findings	40

A cystoscopic examination was made under local anaesthesia about 2 h after a "fatty" meal consisting of an ample portion of butter, egg yolk and creamy milk. "Milky" urine in the bladder may be seen to be resulting either from discharging bulbous vesicles in the bladder wall or from the urine from 1 or both ureteric orifices. Ninety-five cases were examined in this series. Positive findings were present in 55 cases of which bilateral ureteric milky efflux was seen in 13 patients; chylous efflux from the right urinary system in 14 cases and from the left system in 28 cases. No chylous bullae were evident in any of the cases examined.

(*b*) Lymphography

This was done by the pedal route, using lipiodol ultrafluid (May & Baker) as the contrast medium. The following points were noted:

(i) The calibre, number and distribution of the lymphatic vessels;
(ii) The presence and site of lymphatic reflux and fistulisation;
(iii) Patency of the thoracic duct;
(iv) The state of the retroperitoneal lymph nodes in the 24-h film.

This investigation was carried out in 90 patients in this series. Failure to cannulate the pedal lymphatic occurred in 3 patients. The result of the 87 successful lymphograms is analysed in Table 4.

Table 4 Analysis of 87 Lymphograms

Lymphatic vessels:	
Normal	36
Dilated and tortuous	51
Renal lymphatic reflux:	
Left side	30
Right side	16
Bilateral	34
Absent	7
Thoracic duct:	
Patent	73
Not demonstrated	14
Lymph nodes:	
Normal	51
Sparse and/or small	30
Enlarged	6

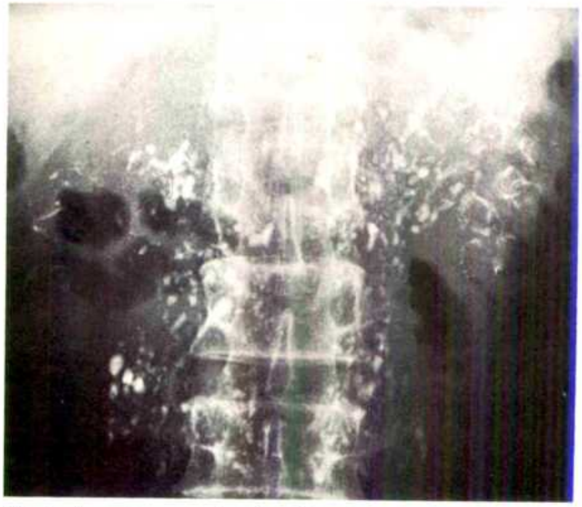


Fig. 1 Lymphogram showing dilated and tortuous lymphatic vessels.

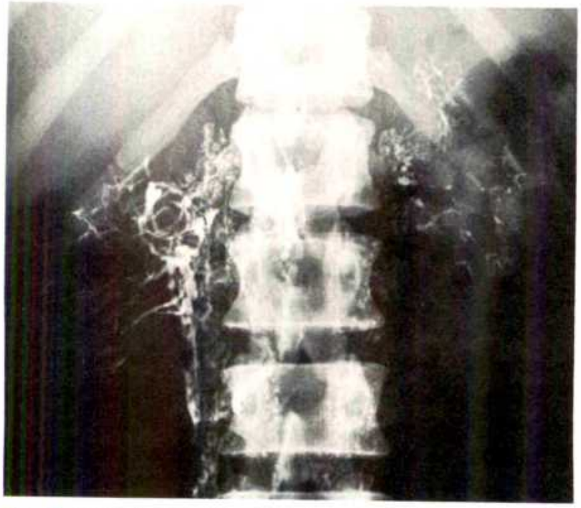


Fig. 2 Lymphogram showing bilateral renal lymphatic reflux.

(1) Normal lymphatic vessels were seen in 36 patients and in 51 cases they were found to be dilated and tortuous (Fig. 1).

(2) Eighty patients showed renal lymphatic reflux of various degrees (Fig. 2). In 34 cases, the reflux was bilateral. In 30 cases, the reflux was on the left side and in 16 cases on the right. No evidence of reflux into the renal lymphatics was seen in 7 cases although the history of chyluria was definite and urine examination for chyle was positive in all these cases.

(3) The thoracic duct was demonstrated to be patent in 73 cases and not well-visualised in 14 cases.

(4) The retroperitoneal lymph nodes were noted to be normal in 51 cases. They were found to be sparse and/or small in 30 cases (Fig. 3) and enlarged and foamy in 6 cases (Fig. 4).

Evaluation of the Upper Urinary Tract

An intravenous urogram was always done as a routine to detect any possible association of other renal abnormalities and the possibility of chylous clots obstructing the ureters. It was found to be normal in all cases except 6, 5 of which showed evidence of tuberculous changes in 1 kidney while the remaining patient showed a radiolucent filling defect which was subsequently shown to be a urothelial carcinoma of the renal pelvis.

Case Report

C.S.L. This was a 60-year-old Chinese male patient with a 1½-year history of heavy haematochyluria with clots and weight loss. Chyle was positive in the urine. An intravenous urogram (Fig. 5) revealed filling defects in the right renal pelvis. Lymphography (Fig. 6) showed the presence of bilateral lymphatico-calyceal fistulisation while cystoscopic examination after a fatty meal showed heavy chylous efflux from the left orifice. The filling defect in the contralateral renal pelvis was obviously due to either a urothelial tumour or chylous clots and the right kidney was therefore explored. The finding was that of a papillomatous tumour of the renal pelvis for which a nephro-ureterectomy was done. The left kidney was subsequently stripped 4 weeks later. Histological study of the lymph nodes and lymphatics revealed no evidence of obstruction or metastases.

Pursuit of Possible Aetiological Factors

Attention is being focused on any possible aetiological factor that may produce derangement in the retroperitoneal lymphatics. The following investigations were done on this aspect:

(*a*) Detection of microfilaria in the blood. This was done by repeated examination of thick blood smears taken at midnight on patients admitted for investigation;

(*b*) Absolute eosinophil count to detect the possibility of parasitic infestation;

(*c*) Histological studies of retroperitoneal lymph nodes and lymphatics. A routine biopsy was taken from an enlarged retroperitoneal lymph node and the resected lymphatics on all patients subjected to surgical treatment.

(*d*) Urine for acid-fast bacilli.

Attempts to detect microfilaria in blood were

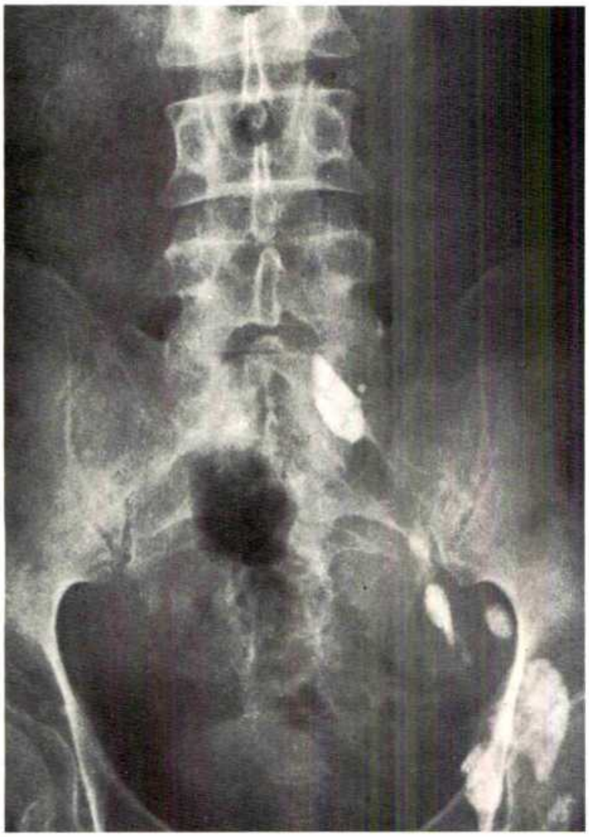


Fig. 3 Lymphogram at 24 h showing sparse and small retroperitoneal lymph nodes.

made on all the 90 patients admitted for lymphographic studies. However, in none of them was the parasite demonstrated although in 2 patients there was history suggestive of filariasis some 20 years ago. Absolute eosinophil count was also within normal limits in the same group of patients. Histological studies of 42 lymphatics and lymph nodes removed at operation showed no evidence of inflammation or fibrosis. All the 5 patients who had radiological evidence of tuberculus kidneys showed positive culture for acid-fast bacilli in the urine.

Treatment

Patients with proven chyluria can be divided into 2 groups:

(1) Mild—these are patients who have "milky" urine intermittently but never clot colic nor clot retention and have no significant loss of body weight. Such patients can usually be managed conservatively by dietary restriction of fat and fatty food.

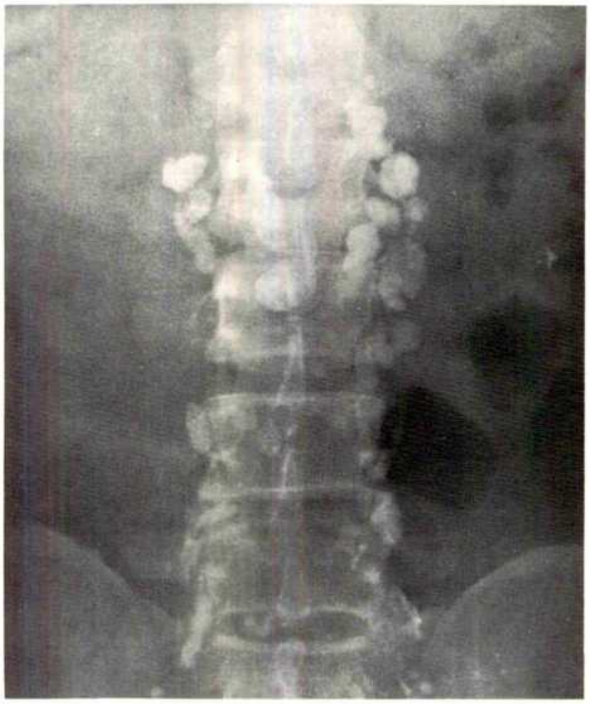


Fig. 4 Lymphogram at 24 h showing enlarged and foamy retroperitoneal lymph nodes.

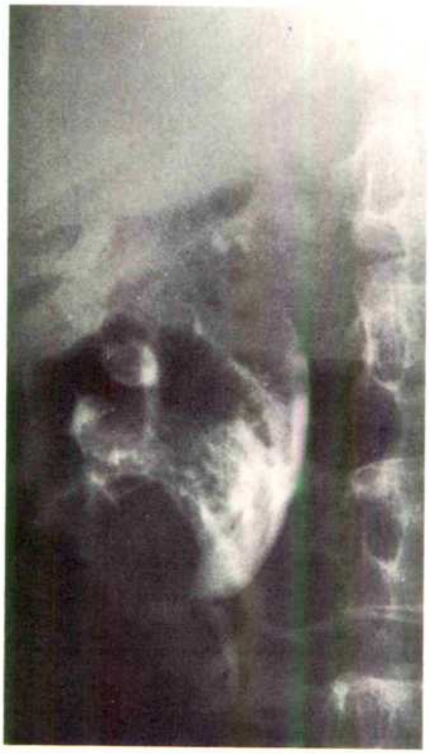
(2) Severe—these are patients who have persistent heavy chyluria often associated with ureteric colic or acute urinary retention and where strict dietary restriction does not alleviate the symptoms. Operative intervention in this group of patients in the form of disrupting the lymphatico-calyceal fistulisation is absolutely essential, not only to prevent progressive debilitation from excessive loss of absorbed nutrient but also to avoid the danger of damaging the upper urinary tract from chylous clot obstructive uropathy.

Operative Procedure

The basic aim in operative treatment is to disconnect the lymphatics from the kidney and upper ureter by stripping the kidney and its pedicle (Lloyd-Davies *et al.*, 1967; Koo and Langenberg, 1969; Mogg and Jones, 1971). Two approaches were used.

1. Retroperitoneal Approach

The kidney is exposed extraperitoneally through the bed of the twelfth rib. Complete mobilisation of the kidney is absolutely essential and care must be taken not to damage the aberrant upper pole



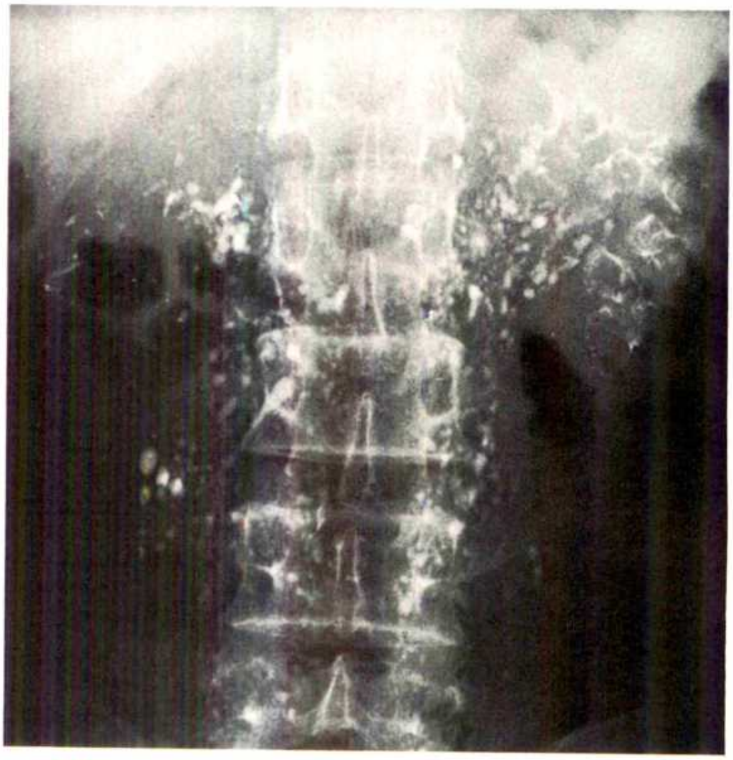


Fig. 5 Intravenous urogram of patient C.S.L. M/60 showing filling defects in the right renal pelvis.

Fig. 6 Lymphogram of patient C.S.L. M/60 showing bilateral renal lymphatic reflux more severe on left side.

artery of the kidney which is fairly common amongst Chinese. The kidney, its pedicle, the renal vessels and the upper ureter are then skeletonised leaving them bare and completely stripped clean of fat and areolar tissue, ligating the lymphatic channels which are always extremely dilated and conspicuous at the origin of the renal vessels. Not uncommonly, the kidney goes into a phase of ischaemia from dissection around the renal artery. This, fortunately, is usually transient and carries no permanent damage as shown by an intravenous urogram taken as a routine within 24 h of the operation.

When both kidneys are involved, stripping is done first on the side with more severe reflux and if symptoms persist the contralateral side is dealt with separately at a different session in a similar manner.

2. Transperitoneal Approach

Alternatively the kidneys can be approached transperitoneally via an abdominal incision. The kidneys are exposed after reflecting the hepatic and splenic flexures of the colon.

Results

Of the 161 cases being followed up the majority responded well to conservative treatment. Only 42 patients required surgical intervention.

Of these 42 cases, unilateral reflux of chyle into the renal lymphatics was seen in 26 cases for which unilateral stripping was performed (14 left, 12 right). Sixteen cases had bilateral reflux for which bilateral stripping was done in 2 cases. In 14 cases where there was evidence of bilateral reflux unilateral stripping was done on the side with heavier chyle leakage. The response was dramatic and no further stripping was deemed necessary for the contralateral side.

Transient ischaemic change was invariably observed in all the kidneys stripped at operation. However, in no case was the renal function impaired permanently as was evidenced by the post-operative intravenous urogram.

No post-operative complications were observed in any case while the lymphatics were stripped via the retroperitoneal approach other than a transient low-grade post-operative pyrexia. All patients left hospital within 10 days. In the patient where a transperitoneal stripping was performed simultaneously on both sides a post-operative ileus of 4 days' duration was observed. This, however, settled spontaneously.

Long-term Results

Seven patients had persistent chyluria after operation. Of these, 4 were demonstrated to be leaking from lymphatico-calyceal fistulae on the contralateral side. They responded well to conservative treatment. One patient was lost to follow-up. In the remaining 2 patients the persistent symptoms were shown to be due to incomplete stripping. Further lymphographic studies on these 2 patients showed that in 1 the upper ureter had not been adequately disconnected from lymphatic connections, and in the other (who had bilateral stripping done simultaneously transperitoneally) residual lymphatico-calyceal fistulae were present (Fig. 7).

A 10-year follow-up of the remaining 35 cases showed that they were chyle free in spite of return to a normal diet. Eleven of these patients had post-operative lymphography. Consistent findings were obtained in that all had complete disconnection of the lymphatic channels from the kidney and the upper ureter and no recannalisation was noticed (Fig. 8).

Discussion

The passage of "milky" urine is not an uncommon complaint in a genito-urinary service in this part of the world. The demonstration of fat globules confirms the diagnosis of chyluria. The absence of fat globules in a single random sample of urine in one who has had a history of "milky" urine does not rule out chyluria nor does it mean that the disease is cured. It is a well-known fact that remission is common and may be for long periods. In this series, for example, only two-thirds of the patients had fat globules in their urine at the first examination. Diagnosis of the remaining patients was only established after repeated urine examination for chyle or by lymphography. Once the diagnosis is established, the approach lies in assessing the severity of the disease and the site of lymphatico-calyceal fistulisation. The severity of the disease could be guided by the symptomatology. In our experience severe chyluria is characterised by:

1. Persistent symptoms;
2. The presence of chylous clots especially with history of clot colic and urinary retention;
3. Significant loss of body weight.

Transpedal lymphography is invaluable in the accurate demonstration of the site of lymphatico-calyceal fistulisation (Callahan *et al.*, 1965; Chen,

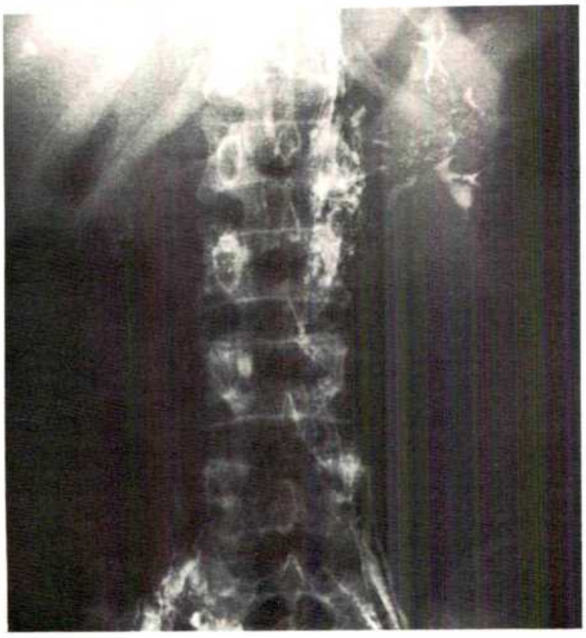


Fig. 7 Post-operative lymphogram of patient with clinical recurrence after stripping showing residual lymphatics in the left kidney.

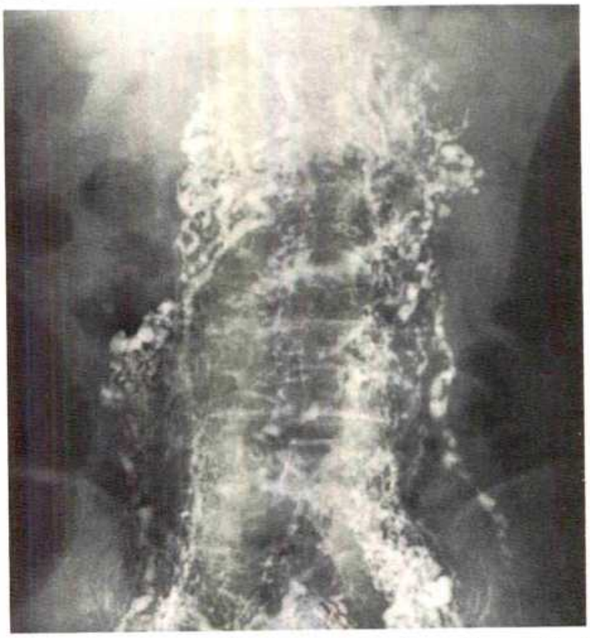


Fig. 8 Post-operative lymphogram of patient without clinical recurrence of chyluria showing complete disconnection of lymphatic channels and no evidence of recannalisation.

1971; Lang *et al.*, 1972), while cystoscopic examination after a fatty meal especially during the phase of acute symptoms, will help in determining the relative severity of involvement of one side of the urinary tract over the other. These 2 investigations therefore determine the side for operation if such is deemed necessary.

Conservative management should always be encouraged. This includes the complete avoidance of fat and fatty products in the diet or by substitution with medium chain triglycerides (MCT) (Hashim *et al.*, 1964). Significant alleviation of symptoms is frequently encountered as remission is not uncommon. In this series only 42 patients out of 161 ultimately required surgery.

Severe chyluria and marked psychological disturbance form the 2 criteria for operative intervention. It is a well-established fact that a meticulous dissection and disconnection of the renal lymphatics is the only satisfactory method of treatment (Lloyd-Davies *et al.*, 1967; Koo and Langenberg, 1969; Mogg and Jones, 1971; Chang *et al.*, 1973). Stripping of the involved kidney, its pedicle and the upper ureter, in our experience, gives consistently good results. Retroperitoneal approach is preferred to the transperitoneal route as better mobilisation of the kidney is possible and more thorough skeletonisation of the renal pedicle could be achieved. In our series, the only case operated via the transperitoneal approach has shown evidence of incomplete disconnection of the renal lymphatic.

Should both kidneys be involved as shown by lymphography, we feel that the side with more severe leakage should be operated on first instead of both sides at the same time. This is because: (1) symptoms may subside after unilateral stripping as is shown in our series; (2) though permanent derangement of renal function or damage to the renal pedicle has not been our experience, this is, however, a potential hazard. Furthermore our experience does show evidence of ischaemia of the kidney during dissection and should both kidneys be thus involved a period of post-operative renal failure may ensue.

The basic reason for the development of dilated and tortuous lymphatic channels towards the kidneys and thus producing fistulae is obscure. The fact that the frequency of the disease is heightened along the filarial belt (Fig. 9) and that other workers have reported a close association (Ray and Rao, 1939; Yamauchi, 1945; Akisada and Tani, 1968; Charters, 1970) have suggested the possibility of lymphatic obstruction by filarial involvement is the basic aetiology. This has not been our experience for none of the 161 cases showed features of elephantiasis although 2 patients gave a past history suggestive of filarial infection. The 90 patients studied by lymphography showed absence of microfilaria in the nocturnal blood smears and absence of eosinophilia. Histo-

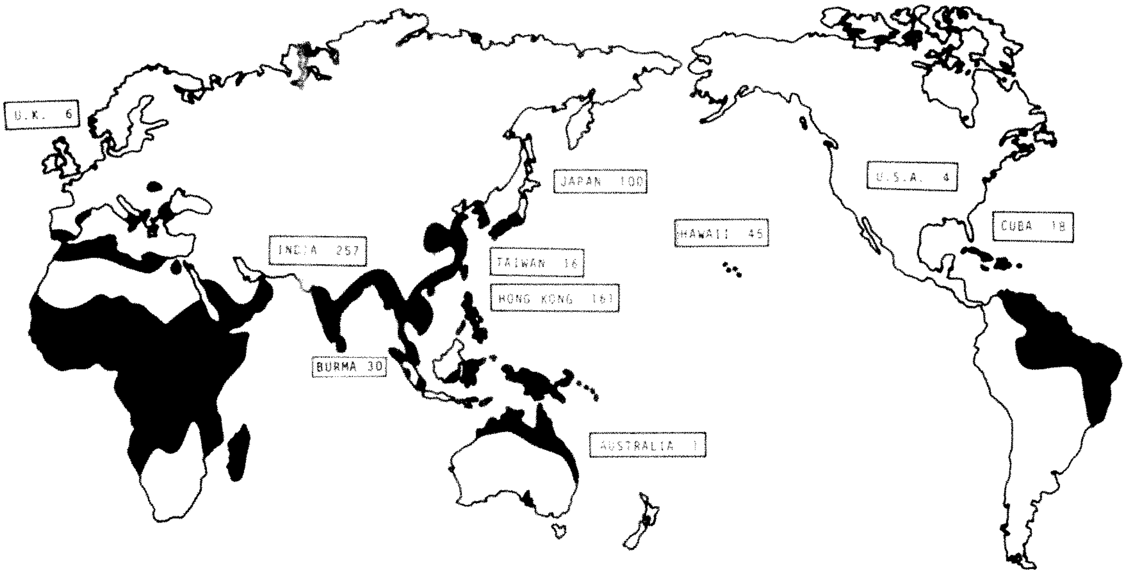


Fig. 9 World distribution of filariasis and reported cases of chyluria.

logical study of lymph node and lymphatic vessels of the 42 patients treated surgically showed no evidence of inflammation or fibrosis.

The singular absence of lymphatic obstruction and yet the presence of dilated aberrant channels may point to congenital abnormalities of the lymphatic system as the basic cause of chyluria (Yamauchi, 1945; Lloyd-Davies *et al.*, 1967; Akisada and Tani, 1968; Ko Ko *et al.*, 1975). The possibility of repeated retroperitoneal infection as a possible aetiology should not be discarded, as the scarring and fibrosis may well lead to derangement of the whole retroperitoneal lymphatic system. Detailed analysis of the association between chyluria and pelvic infection or prostatitis may shed light on the possible aetiology.

Acknowledgement

We wish to thank Professor G. B. Ong for his permission to publish this paper.

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Serum Alphafetoprotein (AFP) in Bilharziasis

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Summary—Two hundred and eighty-four patients of various ages from an endemic area, diagnosed as having bilharziasis by the presence of living *Schistosoma haematobium's* ova in the mid-stream urine sample, have been investigated for the presence of alphafetoprotein (AFP) in the serum.

One hundred and forty-one (49.6%), were positive; no false positives have occurred.

Radioimmunoassay is capable of increasing the positivity rate still further.

The detection of AFP will be of limited value as a screening test in countries where bilharziasis is endemic.

Human bilharziasis is attributed to the pathological effects of infestation by one or other of the species of Schistosoma—*mansoni, haematobium* and *japanicum*. The only species present in Iraq is *S. haematobium* whose ova possess terminal spine and the main habitat is the urinary tract. The disease appears to be widespread in Iraq. Although in the northern part of the country the condition is rare, in the middle and lower parts the incidence and the intensity of the disease are high, especially towards the south. The percentage of infestation in the whole of Iraq is 25.77% (Shamma, 1965).

We began to consider the possibility of the presence of AFP in bilharziasis last year, when we found a positive AFP in 59 cases out of 112 with carcinoma of the bladder, which was complicating untreated childhood bilharziasis. Liver secondaries were excluded in all the 59 cases by liver biopsy at laparotomy (49 cases), liver scan (8 cases), and liver biopsy (2 cases).

Patients and Methods

From an endemic area of the country sera were obtained from 284 individuals (whose ages ranged from 6 to 59 years) all of whom had haematuria but no history of other genito-urinary or general symptoms of disease.

Counter-current electrophoresis (Mawas *et al.*, 1970) was used for the detection and the identification of AFP in the sera, and was performed on cellulose acetate paper (CAM). The pattern of the depressions was described by Kohn (1973). A series of experiments with standards from various commercial sources indicated a sensitivity of 220 to 1000 ng/ml or even higher. Using the AFP provided by Mercia, the presence of 220 ng/ml could still be clearly demonstrated. The positive control sera were calibrated and checked against standard sera and pure AFP, both supplied by Behring and Dakopatts. Liver function tests and liver scan were done in all the 141 positive cases.

Results

AFP was detected in the sera of 141 (53 females, 88 males) out of the 284 patients (49.6%) with bilharziasis only. The liver scan was shown to be normal in all 141 cases with positive AFP. Liver function tests did not show any pathological levels.

Discussion

Hypotheses regarding the role of AFP in foetal development (Smith, 1972), its presence in normal human sera (Ruoslahti *et al.*, 1972) and possible reasons for its reappearance in abnormal amounts in hepatocellular carcinoma, teratocarcinoma (Smith, 1972), carcinoma of the stomach (Alpert *et al.*, 1971), carcinoma of the bladder (Alpert, Pinn and Isselbacher, 1971) and other conditions, have been extensively reviewed. A previous study in Iraq (unpublished data) showed positive AFP in 59 cases of carcinoma of the bladder in which liver metastases had been

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excluded by liver biopsy (49) and liver scan (8 cases). These results correlated with a previous history of untreated bilharziasis which was found in all cases.

We tried to explain these results by assuming that bilharziasis may cause secondary liver fibrosis which may again be responsible for AFP production. The level of gammaglobulin in the serum was increased in 46 cases only, and autoantibodies to liver homogenate were found in 7 cases only, in the total of 141 cases. Unfortunately, this suggestion was not tenable as: 1. local studies in Iraq prove that liver fibrosis secondary to infestation takes a long time to develop (Shamma, 1965); 2. previous studies on the pathogenesis of bilharziasis showed no liver changes; 3. liver scan is normal.

These results may dispute Gitlin's theory (Alpert *et al.*, 1971) which emphasises that embryonic liver and yolk sac are the only tissues capable of synthesising AFP.

The most important point is that in Iraq and all other endemic areas of bilharziasis in the world, these findings—cases of bilharziasis without any co-existing diseases showing positive AFP—underline the failure of the test as a screening method in the diagnosis of other diseases in which the AFP is raised.

Acknowledgements

My great thanks to Professor J. Kohn for his supervision and Miss A. Alsabti for her cooperation.

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Case Reports

Bilateral Ureteric Obstruction Secondary to Reticulum Cell Sarcoma

The urinary tract is usually involved by lymphoma in the form of diffuse kidney infiltration. Bilateral ureteric obstruction by reticulum cell sarcoma is a very unusual phenomenon and only 3 similar cases have been reported (Kaufman, 1962; Brewer *et al.*, 1967; Koziol, 1974).

Case Report

In July 1974 an enlarged left inguinal lymph node was biopsied in a 40-year-old woman. Histological examination revealed a lymphomatous process. The patient was treated with prednisone, vincristine and cyclophosphamide and received a course of radiation therapy of 4000 r to the retroperitoneal region and the left inguinal area.

In April 1975 the patient became anuric. At admission, she presented in very poor condition. Blood urea was 143 mg % and serum creatinine 8.1 mg %. A retrograde pyelogram showed a stricture of the upper right ureter and of the distal left ureter (Fig. 1a). A right lumbotomy was performed and a fusiform firm swelling of the mid-ureter was found. The obstructed part of the right ureter was resected and replaced by a ureteric prosthesis 8 cm in length and 0.5 cm in diameter. Serum creatinine dropped to 1.7 mg % 1 week later and a post-operative intravenous pyelogram showed a functioning right kidney without obstruction (Fig. 1b). Unfortunately, the patient's general condition and renal function deteriorated again and she died 3 weeks post-operatively.

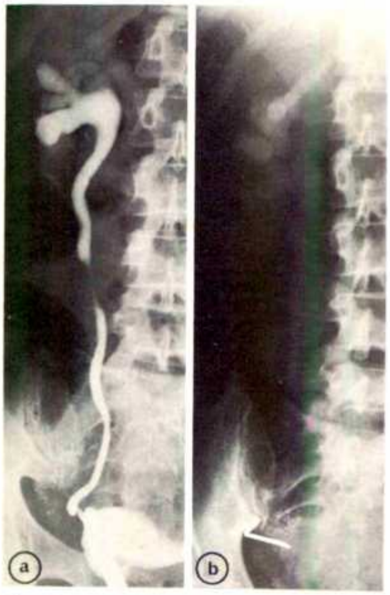

Fig. 1 (a) Retrograde pyelogram discloses an obstruction of the right mid-ureter; (b) intravenous pyelogram 1 week after operation shows marked improvement of right hydronephrosis. The ureteric prosthesis is filled by contrast medium. Traces of former lymphangiography can be seen.

The autopsy showed a poorly differentiated reticulum cell sarcoma infiltrating the retroperitoneum and the lymph nodes. Metastases to skin and ovaries were also observed. The tumour involved the posterior wall of the bladder and completely obstructed the terminal portion of both ureters, below the level of the ureteric prosthesis. The ureteric wall was also involved by the tumour.

Comment

Rather than nephrostomy, ureteric replacement by a prosthesis may be considered in selected cases of malignant ureteric obstruction. It allows a comfortable survival in patients with a short life expectancy. To prevent recurrent ureteric involvement by the malignant process, it seems advisable to use the longest possible prosthesis.

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Ureteric Stricture after Vaginal Ureterolithotomy

O'Boyle and Gibbon (1976) have reported recently on vaginal ureterolithotomy. A late complication 23 years after vaginal ureterolithotomy is presented.

Case Report

A 47-year-old woman was admitted in 1974 with right-sided renal colic. She had had a stone in the lower segment of the ureter removed by transvaginal ureterolithotomy in 1951. Intravenous urogram showed a right-sided hydronephrosis caused by a stricture of the ureter after the previous operation (Fig. 1a). At operation, the right ureter, which was very wide, was dissected retroperitoneally, and a stone lying above a stricture in the intramural part of the ureter was removed. The ureter was transected just above the bladder and reimplanted submucosally into the bladder. The opened bladder was sutured. A Redon drain passed through the urethra was left in the ureter and a Couvelaire catheter in the urethra. At follow-up 2 years after operation (and 25 years after the first operation), the hydronephrosis was greatly reduced, and the right kidney had regained its normal shape. The pelvis and calyces were no longer dilated (Fig. 1b) although the lower segment of the right ureter was still slightly dilated.

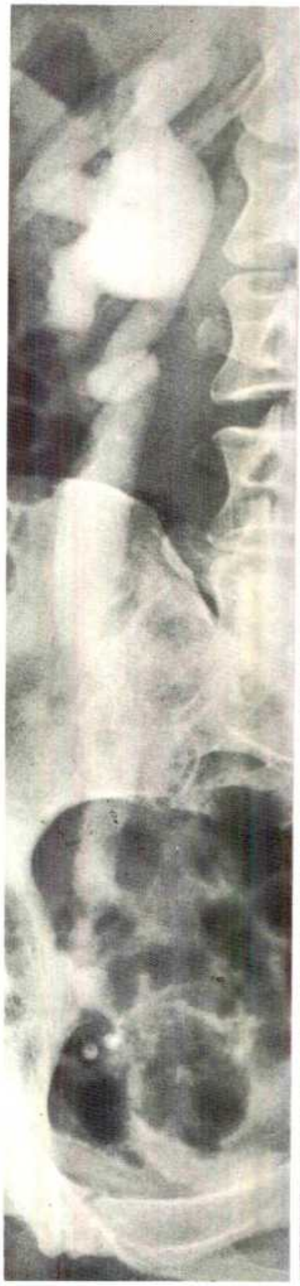

Fig. 1a

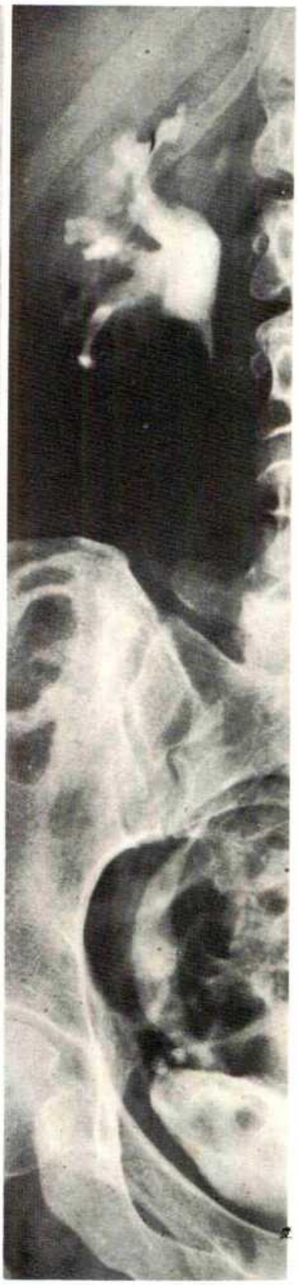

Fig. 1b

Comment

The case illustrates a late complication in the form of ureterohydronephrosis due to ureteric stricture after a transvaginal lithotomy. Reimplantation of the ureter gave good results despite many years' duration of the stricture.

Reference

O'Boyle, P. J. and Gibbon, N. O. K. (1976). Vaginal ureterolithotomy. *British Journal of Urology*, **48**, 231-233.

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Ureterosigmoidostomy (Coffey): 30-year Follow-up

Case Report

A 50-year-old woman (clin. hist. 1247/76) upon whom I had performed a 2-stage ureterosigmoidostomy (Coffey I) 30 years ago because of exstrophy of the bladder was admitted for follow-up examination.

The first operation consisted of implantation of the right ureter into the sigmoid colon retroperitoneally by Coffey's method I on 30 October 1946. The post-operative course was uncomplicated. The left ureter was implanted into the sigmoid on 23 December 1946. On 10 November 1947, cystectomy was performed, with smooth post-operative course. After these operations the patient was able to attend school. She voided urine every 2 to 3 h in the daytime and 2 to 3 times in the night. Urinary continence was satisfactory. Several years later the patient married, and on 20 December 1953 gave birth naturally to a pretty child, and 2 years later to a second child. Both children were healthy and without any structural anomalies. In 1963 she underwent a left pyelolithotomy. At present, intravenous urography shows normal function of both kidneys (Fig.). The left pelvis is somewhat dilated, and the left kidney was somewhat obscured by gas, but early excretion of contrast medium is evident. Blood urea is 35 mg %, and serum creatinine 0.6 mg %. The patient is in good general condition. She voids urine every 2 to 3 h, separately from stools.

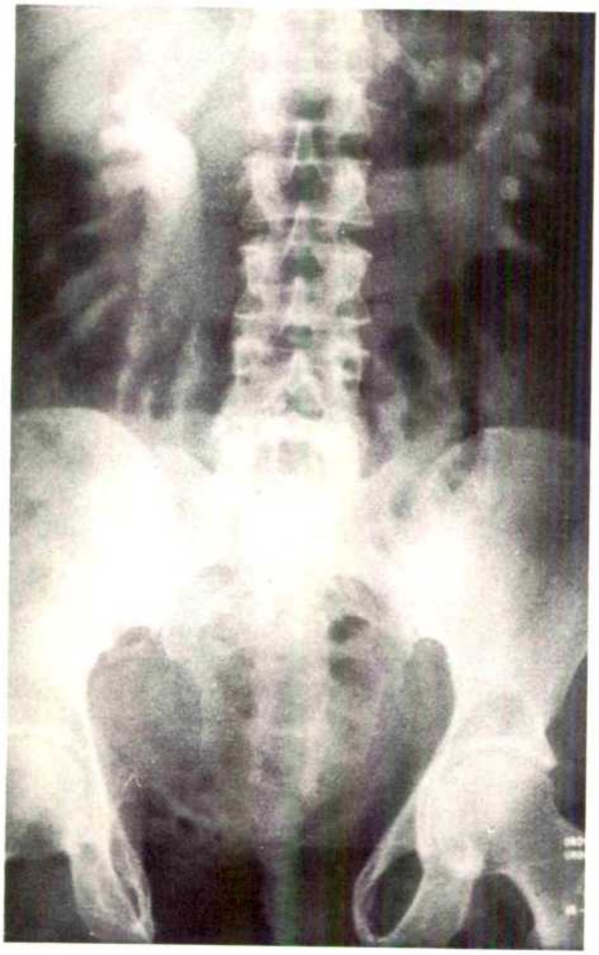

Fig.

The follow-up examination 30 years after the operations showed that results of ureterosigmoidostomy by the method of Coffey are good. There was no recurrence of lithiasis in the left kidney.

Comment

Operative deviation of urine to the sigmoid enabled the patient to lead a normal life, to attend school, and to be socially active. She married and had 2 children.

This case provides additional support for the thesis that in cases of bladder exstrophy, deviation of urine through the sigmoid colon can give good late results.

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Carcinoma in the Bladder Left Behind

Symptoms from a defunctioned bladder may be due to carcinoma and not simple pyocystis.

Case Report

A 39-year-old female, in whom a colostomy had been fashioned in infancy for imperforate anus with sacral agenesis and a neuropathic bladder, had been treated since her teens for recurrent cystitis. Several bladder stones were removed endoscopically. Nine months ago, persistent infection and incontinence necessitated ileal conduit diversion. Cystoscopy revealed marked inflammation and trabeculation. Suprapubic discomfort and a purulent discharge from the bladder were unrelieved by vesico-vaginostomy. Cystectomy was performed 6 months after diversion, when the bladder was found to contain a large ulcerated and infiltrating transitional cell carcinoma within which were areas of squamous metaplasia (Figs. 1 and 2). There was extensive squamous metaplasia of the remaining epithelium.

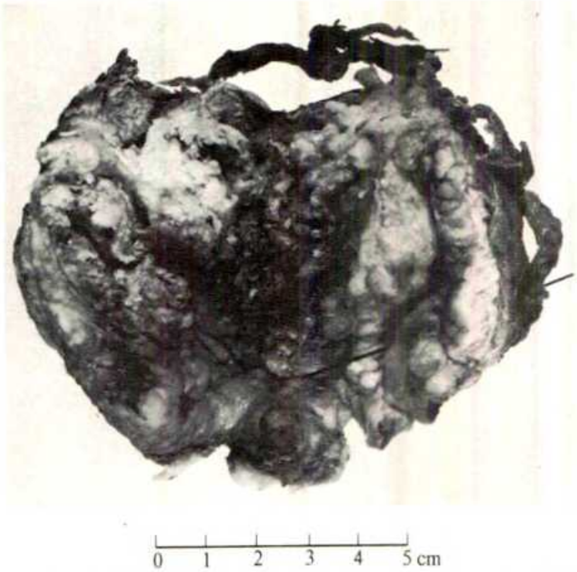

Fig. 1 Cystectomy specimen showing bulky partially ulcerated tumour (probe in left ureteric orifice).

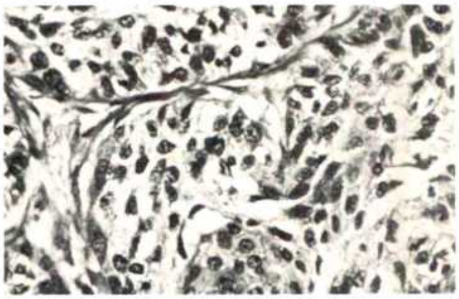

Fig. 2 Foci of squamous metaplasia in transitional cell carcinoma of bladder. H & E. Magnification ×40 (enlargement ×4).

Comment

This is the third recorded case of carcinoma developing in a defunctioned bladder. The histology of this and previously reported cases (Silber, 1973) all showed squamous features. There is a high incidence of squamous metaplasia in chronically inflamed bladders (Polsky *et al.*, 1976) but although progression to carcinoma remains unproven, such patients may be at risk. Periodic cystoscopy, bladder biopsy or cytological examination of the defunctioned bladder are advised, particularly where symptoms occur and conservative management is contemplated.

Acknowledgements

I would like to thank Mr D. Innes Williams for permission to report this patient and Dr K. M. Cameron for helpful discussion.

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Primary Actinomycosis of Kidney Presenting with Reno-colic Fistula

Primary actinomycosis of the kidney is an uncommon disease. Since the report of 28 cases by Baron and Arduino (1949), sporadic reports have been published by various authors (Cohen, 1943; Willson-Pepper, 1951; Anhalt and Scott, 1970).

Case Report

L.P., a 59-year-old Chinese housewife, had her mildly inflamed appendix removed as an emergency. Post-operatively, she became anuric.

Plain X-ray of the abdomen revealed opacities resembling stones in the region of the left kidney and lower right ureter. Haemodialysis was performed and bilateral ureteric catheterisation was attempted but failed. In view of the possible right ureteric stone a right nephrostomy was done and her blood urea fell to 56 mg % within 5 days.

Two weeks after appendicectomy she developed wound infection and an intestinal fistula. Barium enema showed multiple fistulae at the splenic flexure (Fig.). On re-exploration, a small bowel fistula found near the ileo-caecal junction was closed. The entire colon was found to be normal with no demonstrable fistula at the splenic flexure. Repeat barium enema also failed to show the splenic fistulae. Further urological investigation revealed a patent right ureter and a normally functioning right kidney. The left kidney was non-functioning and containing numerous stones.

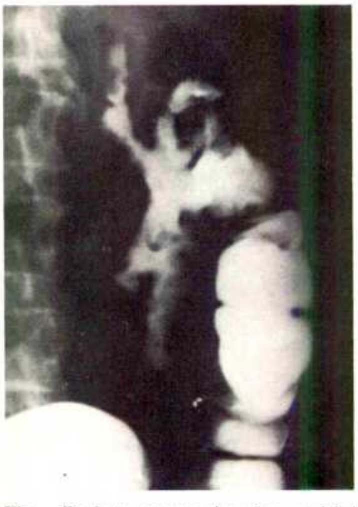

Fig. Barium enema showing multiple fistulae at the splenic flexure.

The left kidney was explored and was found to be small and pyelonephritic with multiple uric acid stones. A fistula lined with granulomatous tissue was demonstrated from lower calyx of the kidney to the splenic flexure of the colon. Posteriorly multiple sinus tracts extended into the psoas muscle and in 1 of the tracts stones were found. Left nephrectomy was done. The fistula was excised from the splenic flexure and the colon repaired.

Histology showed chronic inflammatory granulation tissue with colonies of actinomycosis. The kidney parenchyma showed changes of pyelonephritis with secondary effects of arteriolonephrosclerosis and arteriosclerosis.

Post-operatively the patient was treated with soluble penicillin 8 megaunits daily intravenously and streptomycin 1 g daily intramuscularly and recovery was uneventful.

Comment

Actinomycosis occurs most commonly in the face, neck, lung and ileo-caecal regions. Primary involvement of the kidneys is rare.

Reno-colic fistula is again rare and its occurrence from actinomycosis of the kidney has never been recorded.

For treatment, combined surgical removal and long-term antibiotics are required.

Acknowledgement

We are grateful to Professor G. B. Ong for allowing us to document this patient.

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An Unusual Presentation of Renal Carcinoma

The clinical manifestations of renal carcinoma are many and varied. We describe here a patient who presented with skin metastases.

Case Report

A 65-year-old man was referred in January 1977 with a 3-month history of a warty growth on his scrotum. This was his only symptom when he was first seen. On examination there was a 1.5 cm diameter ulcerated lesion, grey in colour in the scrotal skin (Fig.), at the base of which were 3 red-purple pedunculated nodules. There was a similar nodule on his upper lip. Excision biopsy of these nodules was performed in February 1977. The histological appearance was typical of renal cell carcinoma (clear cell type), although at the time diagnoses of pyogenic granuloma, kerato acanthoma and amelanotic melanoma were entertained. Subsequent IVP, ultrasound and arteriogram confirmed the diagnosis of renal cell carcinoma. Nephrectomy was performed on the 15 March 1977. The tumour was confined within the kidney capsule.

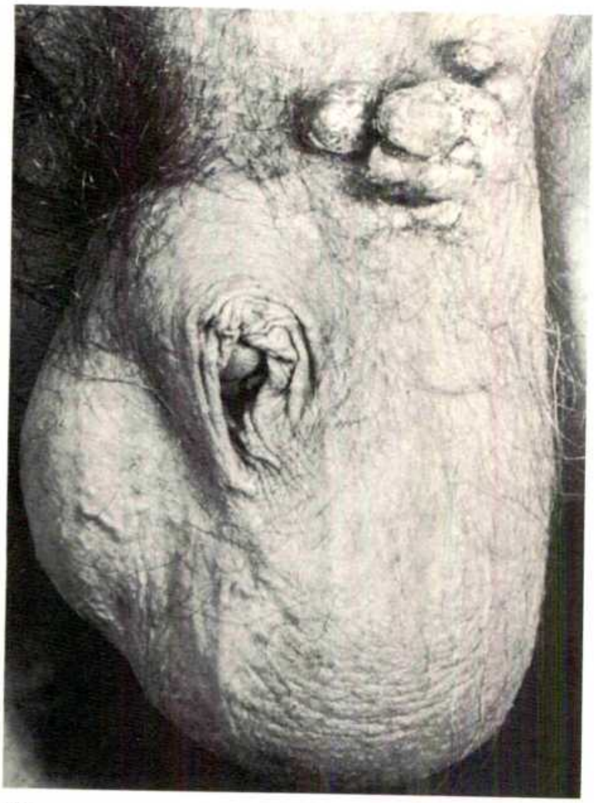

Fig.

Discussion

In a review of 309 cases Skinner *et al.* (1971) noted that 10% of patients presented with clinical symptoms secondary to their metastases. However, the commonest sites for metastases were lung, bone, regional nodes and liver in that order. Cutaneous metastases occur in about 3% of all cases of renal tumours (Scorer, 1951), and in a post-mortem study by Hajdu and Thomas (1967) no skin metastases were noted. Rarely is a skin nodule the first manifestation of the disease.

Acknowledgement

We would like to thank Mr Philip Powley for permission to publish details of a patient under his care.

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The Authors

Anthony Ward, Kent and Canterbury Hospital, Kent.
Neil Soni, Department of Surgery, Princess Margaret Hospital, Swindon.

Renal Carcinoma in a Horseshoe Kidney

Case Report

An 84-year-old male presented with a 3-day history of right lower abdominal pain and haematuria. The excretion urogram showed a horseshoe kidney with absence of contrast in the right element. Arteriography showed abnormal vascularity and pooling of contrast medium in a right upper pole tumour.

Through a midline transperitoneal incision a right radical nephrectomy/isthmectomy was performed (Fig.). Pathology showed clear cell renal carcinoma. Thirty months after surgery the patient is well, free of locally recurrent or metastatic tumour.

Comment

Renal carcinoma in a horseshoe kidney is rare. This is the thirty-ninth case reported. Radical nephrectomy and total excision of the isthmus to the adjacent pole of the opposite kidney were performed. Early ligation of the vessels and isthmectomy conform to the principles of radical cancer surgery, and may reduce the incidence of haemorrhage and urinary fistulae often seen in surgery on horseshoe kidneys.

Thirty patients have undergone radical surgery for carcinoma in a horseshoe kidney (Blackard and Mellinger, 1968; Redman and Mobley, 1973) and follow-up data are available in 18. Sixteen survived 1 to 84 months free of residual, locally recurrent or metastatic tumour. Radical excision of renal carcinoma from the tumour-bearing portion of a horseshoe kidney is indicated. Prolonged survival and potential cure may sometimes be expected.

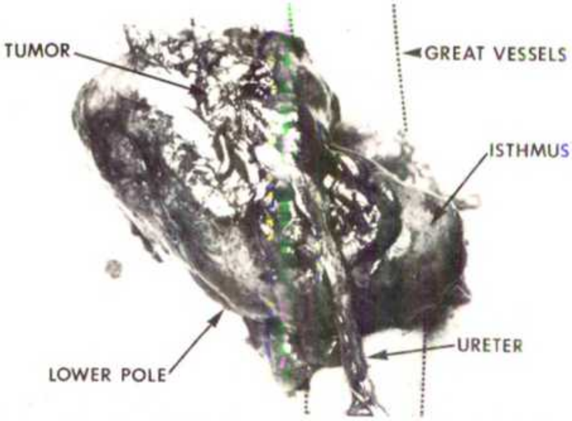

Fig. Surgical specimen showing isthmus overlying the great vessels and upper pole tumour. Ureter passes anterior to the isthmus.

Acknowledgement

The author is grateful to Dr Raimonds Gailitis, Grant Hospital, Chicago, for referring this patient.

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The Author

Leon G. Lome, Division of Urology, Michael Reese Hospital and Medical Center and Grant Hospital, Chicago, Illinois 60616.

Massive Scrotal and Occult Preputial Metastases from Carcinoma of the Prostate

A case of prostatic carcinoma with massive scrotal metastases and clinically unsuspected preputial metastasis is presented.

Case Report

W.E., a 73-year-old black male, underwent bilateral orchiectomy in July 1969 for prostatic adenocarcinoma with metastases to the left inguinal nodes. He was placed on stilboestrol in February 1974 for painful, extensive skeletal metastases. He also noted a painful, gradually increasing scrotal mass in February 1974, which on incisional biopsy elsewhere in May 1974 revealed metastatic adenocarcinoma. The pertinent physical findings were: redundant, oedematous foreskin which could not be retracted over the glans penis (Fig.). There were several small, firm, tender nodules in the skin of the right hemiscrotum and a 9 x 8 x 5 cm, nodular, tender, ulcerated greyish-yellow mass of soft to hard consistency occupying the left hemiscrotum and intimately adherent to the overlying skin. Serum acid phosphatase was 1200 units with prostatic fraction of 340 units. Bone survey revealed extensive osteoblastic metastases.

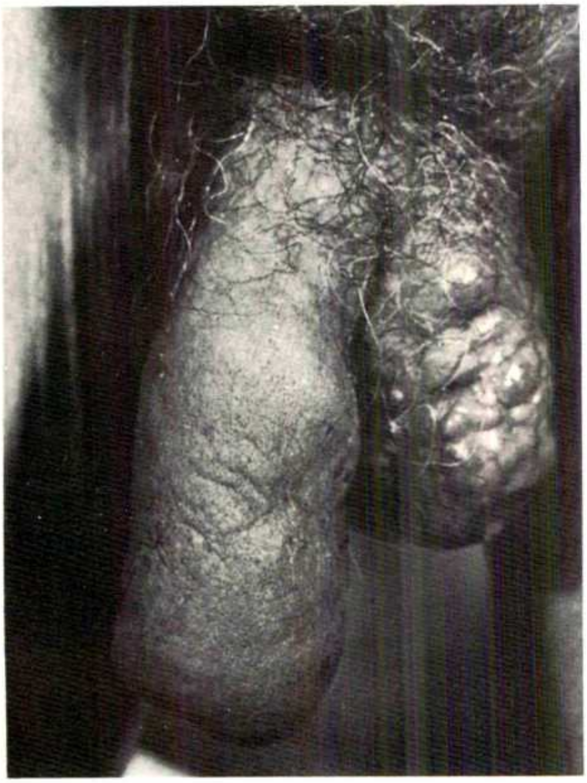

Fig.

In July 1974 a radical excision of the scrotum and circumcision were performed. The pathological diagnosis was metastatic adenocarcinoma involving both scrotum and foreskin. Though there was good local palliation and no local recurrence following surgery, the patient's condition gradually deteriorated and he died of extensive metastases in February 1975.

Comment

Cutaneous metastasis from carcinoma of the prostate is rare and is considered a late manifestation of the malignant disease indicating widespread tumour dissemination with a poor prognosis and early fatal termination.

About 29 cases of cutaneous metastases from prostatic carcinoma have been reported (Delima *et al.*, 1973). Although any part of the skin may be involved, lower abdomen, genitalia (mostly scrotum), and groin are the more frequent sites of involvement.

One other case of preputial metastasis from prostatic carcinoma was reported by Tan and Vishniavsky (1971).

Acknowledgement

Photographic assistance of Mr Donald L. Kluck.

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138 Ureterosigmoidostomy (Coffey): 30-year Follow-up
Stefan Wesolowski

139 Carcinoma in the Bladder Left Behind
Ian A. Aaronson

140 Primary Actinomycosis of Kidney Presenting with Reno-colic Fistula
H. H. Y. Yu, C. M. Yim and C. H. Leong

141 An Unusual Presentation of Renal Carcinoma
Anthony Ward and Neil Soni

142 Renal Carcinoma in a Horseshoe Kidney
Leon G. Lome

143 Massive Scrotal and Occult Preputial Metastases from Carcinoma of the Prostate
Biswanay Ray, Roohollah Sharifi and Samuel S. Clark

144 Conferences and Courses

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April 1978 Volume 50 Number 2

Original Articles

73 Renal Mobility in Women Attending a Pyelonephritis Clinic and in Controls
W. N. T. Thomson, J. A. Innes, J. F. Munro, A. M. Geddes, R. J. Prescott and J. McC. Murdoch

76 Diuresis Renography in Equivocal Urinary Tract Obstruction
P. H. O'Reilly, H. J. Testa, R. S. Lawson, D. J. Farrar and E. Charlton Edwards

81 Cytological Changes due to Urinary Calculi
M. E. Beyer-Boon, L. H. R. I. Cuypers, H. J. de Voogt and J. A. M. Brussee

90 Exstrophy of the Bladder: Treatment by Trigonosigmoidostomy—Long-term Results
W. Gregoir and C. C. Schulman

95 The Incidence and Consequences of Damage to the Parasympathetic Nerve Supply to the Bladder after Abdominoperineal Resection of the Rectum for Carcinoma
J. W. Fowler, D. N. Bremner and L. E. F. Moffat

99 Experience with Anteromedian (12 O'Clock) External Urethral Sphincterotomy in 100 Male Subjects with Neuropathic Bladders
W. F. Whitmore, III, B. A. Fam and S. V. Yalla

102 The Management of Indwelling Catheters
J. C. Brocklehurst and Susan Brocklehurst

106 Diagnostic Catheterisation and Bacteriuria in Women with Urinary Incontinence
Steen Walter and René Vejlsgaard

109 Should Patients be Shaved Prior to Transurethral Surgery?
Ian Fraser, Symon MacPherson and Angelos Panagakis

111 Procarbazine (Natulan) in the Treatment of Peyronie's Disease
R. J. Morgan and J. P. Pryor

114 Surgical Management of Impotence using the Inflatable Penile Prosthesis: Experience with 103 Patients
William L. Furlow

118 The Thermographic Characteristics of Varicocele: An Analysis of 65 Positive Registrations
Reginald Monteyne and Frank Comhaire

121 Adenomatoid Tumour of the Epididymis: Histochemical and Ultrastructural Study of 2 Cases
Manuel Nistal, Félix Contreras and Ricardo Paniagua

126 Chyluria—a 10-year Follow-up
Henry H. Y. Y., Henry Ngan and C. H. Leong

134 Serum Alphafetoprotein (AFP) in Bilharziasis
Elias A. K. Alsabti

Case Reports

136 Bilateral Ureteric Obstruction Secondary in Reticulum Cell Sarcoma
M. Vandendris, C. C. Schulman and P. Potvliege

137 Ureteric Stricture after Vaginal Ureterolithotomy
Stefan Wesolowski

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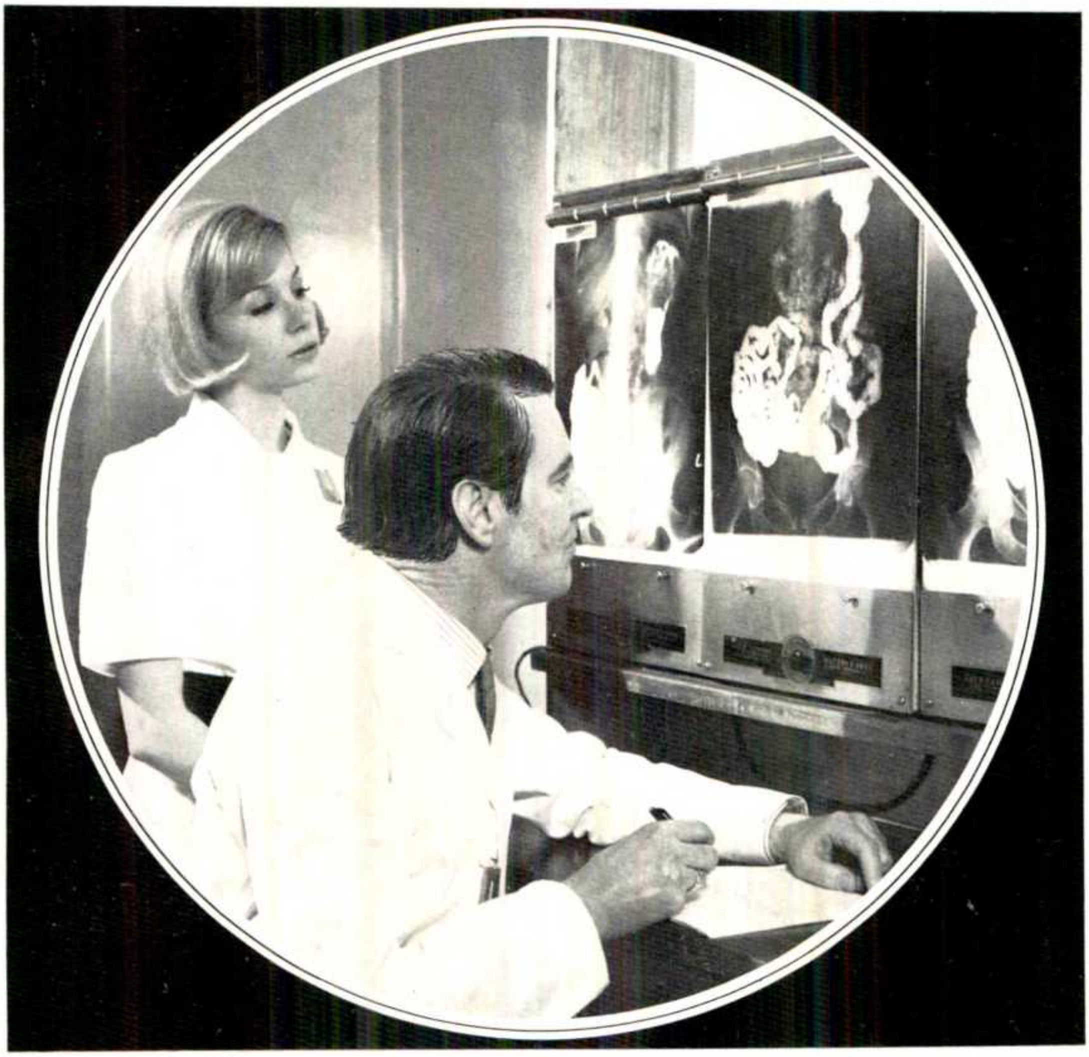

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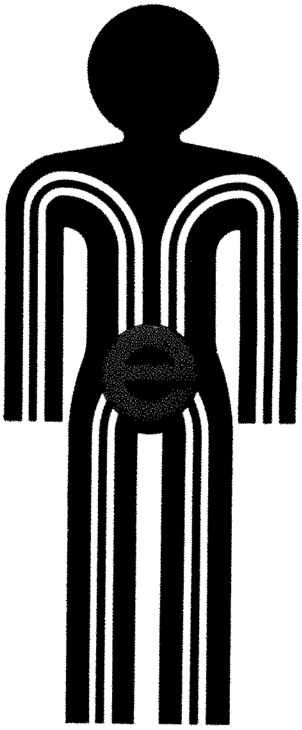

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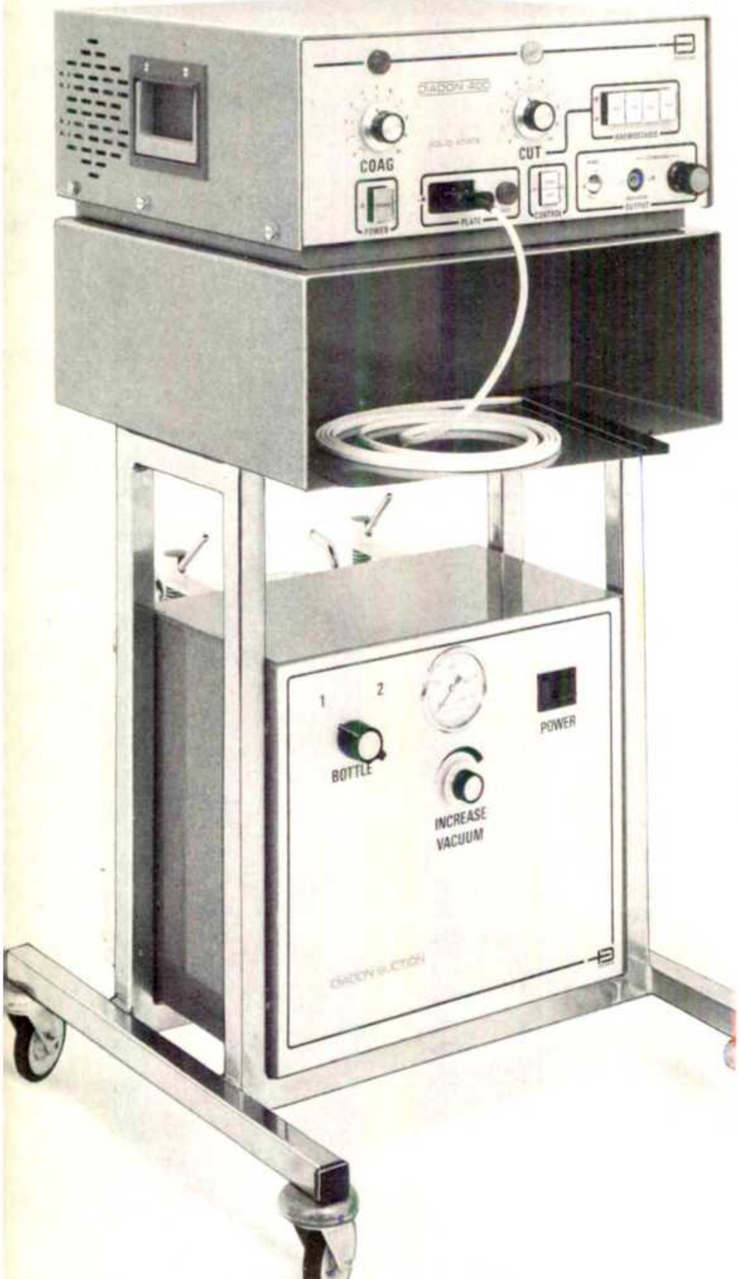

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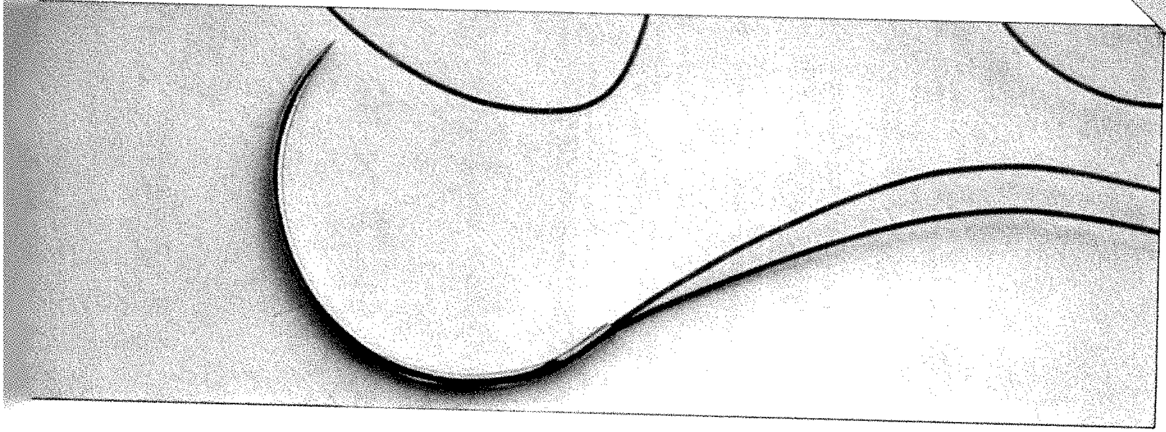

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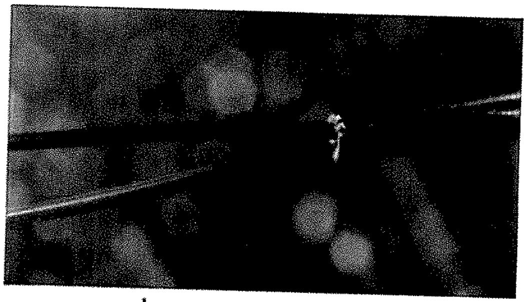

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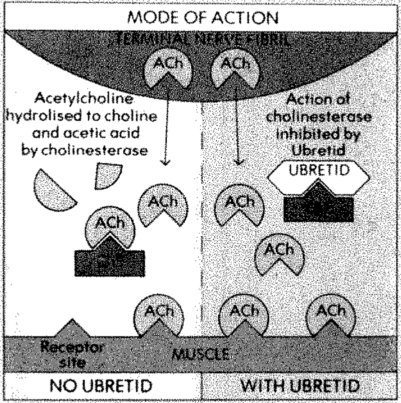
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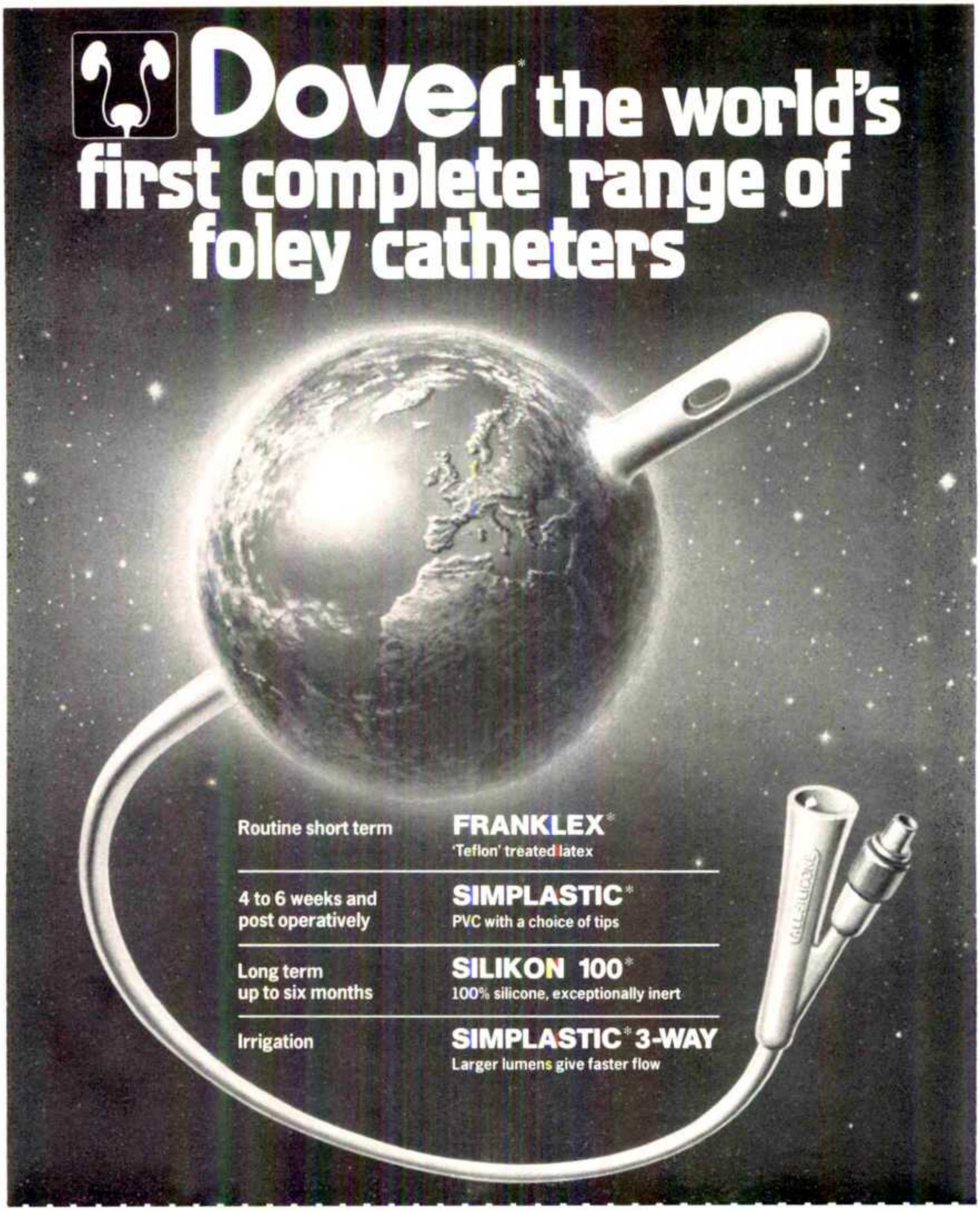

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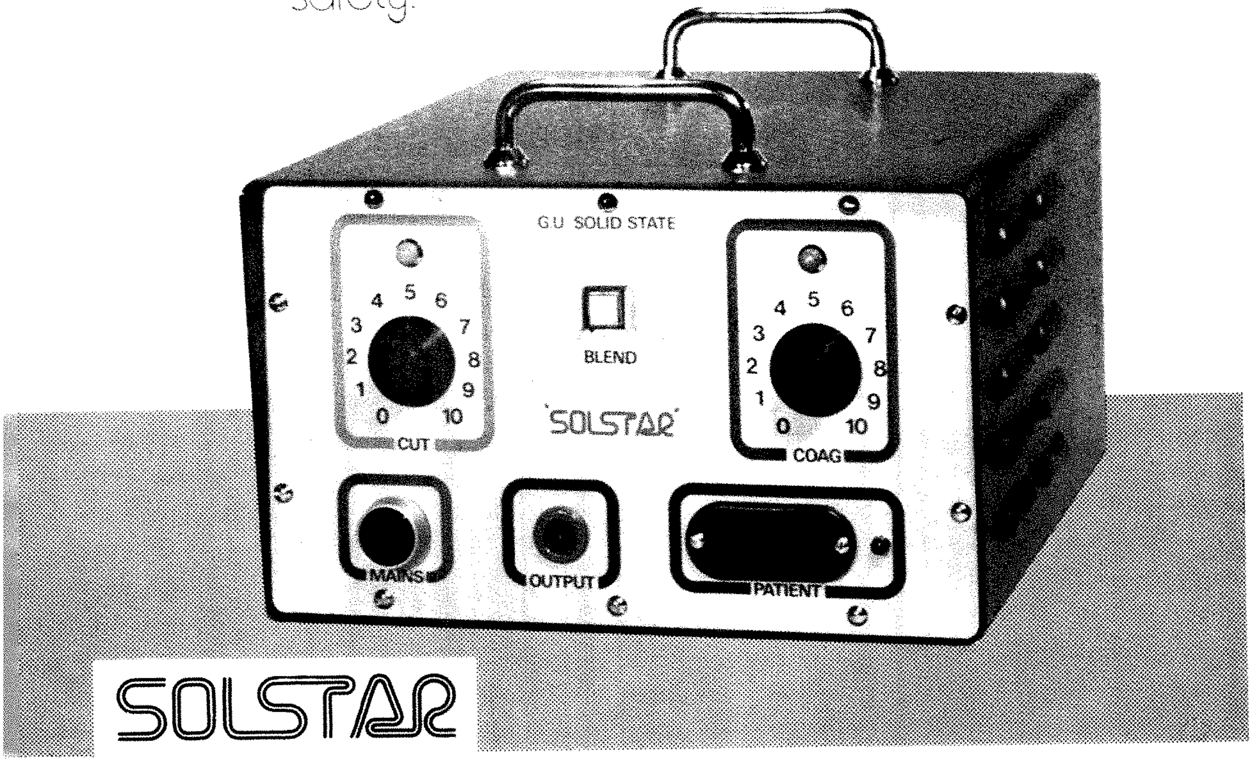

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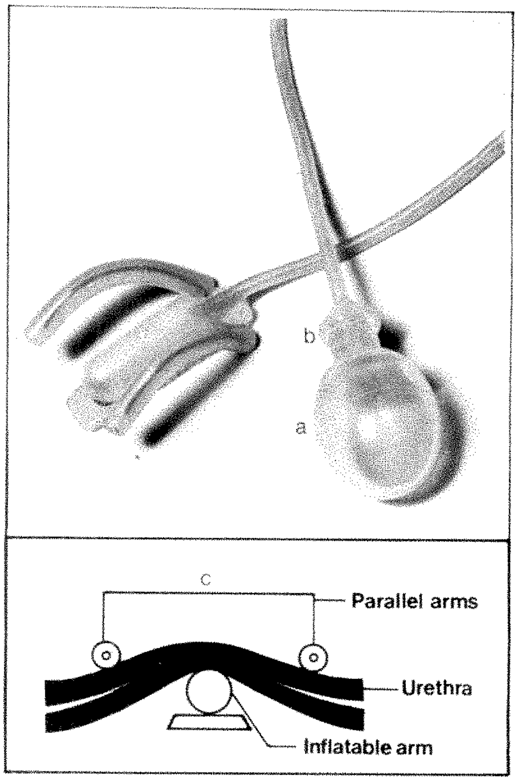

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Functional Obstruction of the Ureter and Renal Pelvis. A Histological and Electron Microscopic Study

J. A. GOSLING and J. S. DIXON

Department of Anatomy, University Medical School, Manchester

Summary—Histological, histochemical and electron microscopic techniques have been used to compare dilated and normal calibre segments of ureter and renal pelvis in cases of idiopathic hydronephrosis and primary obstructive megaureter. In both conditions a marked increase in collagen and elastic tissue occurs in the wall of the distended segment and this infiltration extends throughout the proximal dilated ureter and renal pelvis.

Evidence is presented to show that in the dilated segment, smooth muscle cells are directly involved in the synthesis of connective tissue elements. These findings support the view that the primary anomaly in idiopathic hydronephrosis and primary obstructive megaureter can be attributed to a malfunction of smooth muscle cells in the ureter and renal pelvis. However, the possibility remains that the changes in smooth muscle are secondary and have been induced by obstruction and distension caused in these pathological conditions by unknown aetiological factors.

Of the many theories on the aetiology of idiopathic hydronephrosis and primary obstructive megaureter the most recent has been based upon data obtained using the electron miscroscope. Notley (1968) first applied this method in idiopathic hydronephrosis and described a marked increase in the collagen component of the narrowed pelvi-ureteric segment. This was considered the physical cause of the obstruction by preventing distension of the affected part of the ureter during diuresis (Notley, 1971). In a subsequent study of primary obstructive megaureter (Notley, 1972), a similar accumulation of collagen was proposed as the underlying anomaly responsible for the condition. Hanna *et al.* (1976) used both light and electron microscopic techniques in studies on functional ureteric obstruction and described a similar infiltration of collagen around and between smooth muscle cells in the obstructed segment. In addition these workers described secondary changes, the smooth muscle cells showing evidence of atrophy with disruption or attenuation of nexuses and an excessive accumulation of collagen fibres between the cells. These features were most apparent immediately above the narrowed segment, becoming less obvious in samples obtained from more proximal parts of the dilated ureter and/or pelvis.

During the course of a study employing radioisotope renography to evaluate the functional activity of the upper urinary tract (O'Reilly *et al.*, 1978) tissue from the ureter and renal pelvis has been examined histochemically and with light and electron microscopy. The results obtained in cases of idiopathic hydronephrosis and primary obstructive megaureter differ in a number of respects from those described previously.

Materials and Methods

Material was obtained from 15 patients with idiopathic hydronephrosis and from 6 cases of obstructive megaureter. In the former group, 14 specimens consisted of part of the renal pelvis in continuity with the pelvi-ureteric segment and the proximal portion of the ureter. The other case underwent nephrectomy, providing the kidney, the pelvis and part of the ureter for examination. Of the specimens from cases of primary obstructive megaureter 4 consisted of the narrow segment with a portion of adjacent ureter and 2 comprised kidney, pelvis and ureter in continuity. A kidney, pelvis and ureter removed for hypernephroma were used for comparison as control. Tissue samples were removed and processed for electron microscopy (see below). Each nephrectomy specimen was subdivided and tissue for electron microscopy removed from the region of attachment of the minor calices to the renal paren-

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Accepted for publication 9 December 1977.

chyma, the calices, the renal pelvis, the ureter and the zone of constriction. Samples for electron microscopy from pelvi-ureteric and megaureter specimens were obtained in a manner similar to that described by Hanna *et al.* (1976). In each case, tissue was removed from the obstructed segment and from sites proximal and distal to this zone. All remaining tissues were processed for light microscopy as described below.

Light Microscopy

Tissue blocks were orientated on cryostat tissue holders, rapidly frozen in 2-methylbutane, cooled in liquid nitrogen and stored at −80°C until required. Specimens were then transferred to a cryostat at −25°C internal temperature and serial sections, 10 to 20 μm in thickness, were prepared. Sections were mounted on glass slides and those required for histological purposes processed using Masson's trichrome technique. The method described by Gomori (1952) was employed for tissue cholinesterases. In selected sections, acetyl- and pseudo-cholinesterases were distinguished using the specific inhibitors TIPA (tetraisopropylpyrophosphoramide) and 1,5-bis-(4 alhydimethyl - ammonium - phenyl) - pentane- 3 - one dibromide. Some sections were processed for tissue catecholamines using a fluorescence method similar to that described by Spriggs *et al.* (1966). This technique was also used to determine the distribution of autofluorescent elastin within the tissue sections.

Electron Microscopy

Tissue for electron microscopy was subdivided into blocks approximately 1 mm cube prior to fixation in either 1% osmium tetroxide in acetate-veronal buffer at 4°C and pH 7.3 for 1 h (Palade, 1952), or 5% glutaraldehyde in 0.1 M sodium cacodylate buffer at 4°C and pH 7.3 for 2 h (Sabatini *et al.*, 1963). Using the latter, tissues were post-fixed in 1% osmium tetroxide for ½ h. Following fixation, tissue blocks were dehydrated in ascending concentrations of ethyl alcohol and embedded in epoxy resin with the aid of propylene oxide. Sections cut with glass knives and a Reichert OmU3 ultramicrotome were mounted on copper grids, double stained with alcoholic uranyl acetate (Watson, 1958) and lead citrate (Reynolds, 1963) and examined in a Philips EM300 electron microscope.

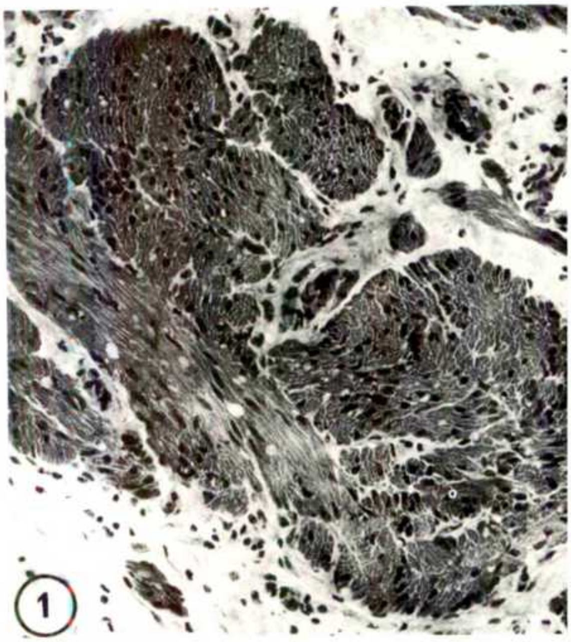

Fig. 1 Compact smooth muscle bundles obtained from t non-dilated segment of ureter in a case of idiopathic hydr nephrosis. Note the minimal amount of connective tiss between the cells within each muscle bundle (×250).

Results

The light and electron microscopic findings we the same in idiopathic hydronephrosis and primary obstructive megaureter. The essenti features common to both conditions will be de cribed.

Light Microscopy

The general arrangement of muscle bundles pelvis and ureter was the same in all tiss examined, whether from wide or normal calib regions. Muscle bundles were continuous fro dilated to normal ureter across the "narrow zone and no preponderance of circularly orie tated muscle was noted in any region. In trichror preparations the distribution of connective tiss in the normal calibre ureter below the obstructi lesion (Fig. 1) was identical to that in norm ureter. However, an abrupt increase in connecti tissue began in the junctional region between t normal calibre and the dilated ureter and extend throughout the proximal part of the ureter a renal pelvis. This additional connective tiss increased the thickness of the lamina propria a extended into the muscle coat between mus bundles (Fig. 3), separating individual smoc

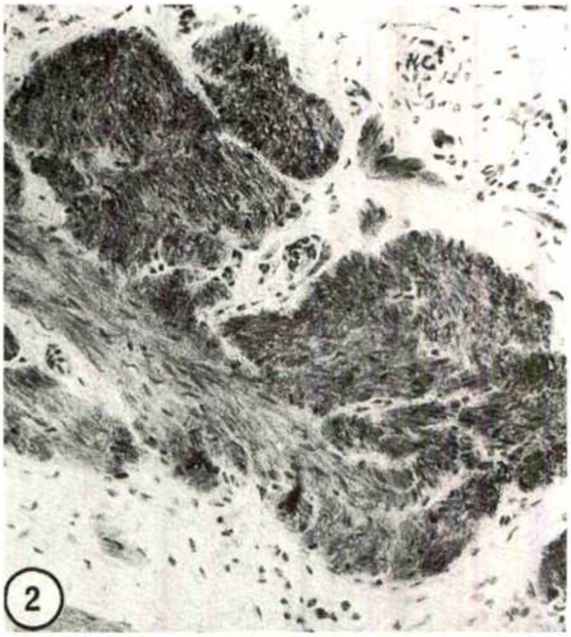

Fig. 2 This adjacent section to that shown in Fig. 1 demonstrates the distribution of non-specific cholinesterase in the smooth muscle coat. Enzyme reaction product is evident in the cells forming each of the muscle bundles. Compare with Fig. 4 (×250).

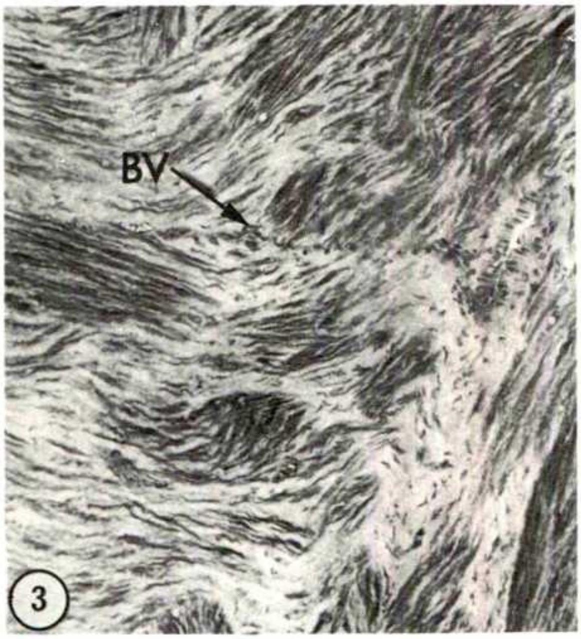

Fig. 3 Section from the dilated renal pelvis of the case illustrated in Figs. 1 and 2. Large amounts of connective tissue extend into the muscle bundles and separate individual smooth muscle cells from one another. BV, blood vessel (×250).

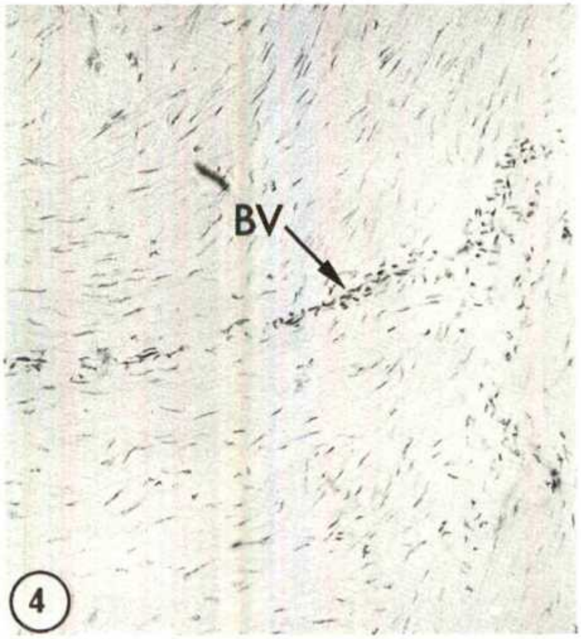

Fig. 4 In this adjacent section to that shown in Fig. 3, the smooth muscle cells are almost devoid of non-specific cholinesterase activity. Note the blood vessel (BV) also shown in Fig. 3 (×250).

muscle cells from their neighbours. This infiltration occurred throughout all parts of the ureter and renal pelvis above the "narrowed" segment. The smooth muscle of the pelvis and ureter in the control specimen and that of the ureter distal to the dilated segments (Fig. 2) was rich in pseudo-cholinesterase. In contrast, pseudo-cholinesterase activity was markedly reduced in the smooth muscle within the wall of the dilated ureter and renal pelvis (Fig. 4) and within the muscle bundles infiltrated by collagen. In all specimens, whether of normal or dilated ureter, acetyl-cholinesterase positive nerves and catecholamine containing nerves had a similar distribution and arrangement. Both acetyl-cholinesterase and catecholamine containing nerves were exceedingly sparse in specimens from the proximal part of the ureter and renal pelvis (Figs. 2 and 4), but became more common in the juxtavesical region.

The fluorescence technique was also employed to study the arrangement of autofluorescent elastin fibres. In the normal calibre ureter numerous fibres were observed running between the muscle bundles and extending into the lamina propria and adventitia (Fig. 5). In contrast, a marked increase in elastin fibres and filaments occurred at the site of dilatation and extended

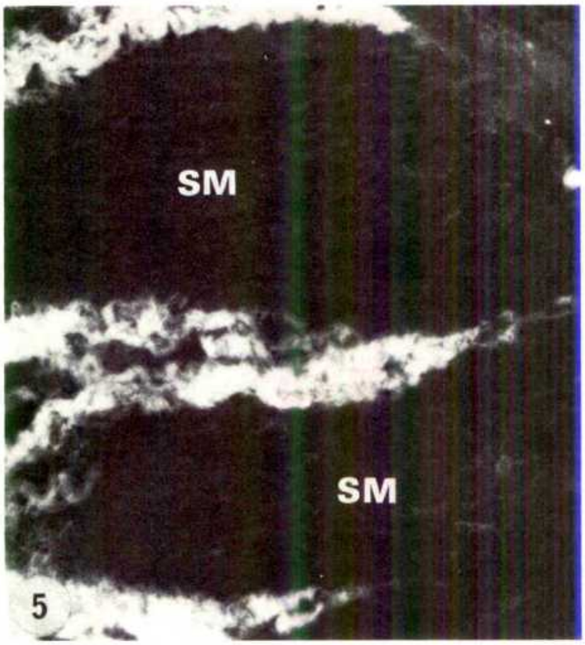

Fig. 5 Using the fluorescence technique, autofluorescent elastic fibres are seen to be mainly confined to the connective tissue separating the compact smooth muscle bundles (SM) in this specimen obtained from a non-dilated segment of ureter. (×300).

from this region throughout the proximal portion of the ureter and renal pelvis. In the dilated portion fine elastin filaments were common between the individual cells which comprised the smooth muscle bundles (Fig. 6).

Electron Microscopy

The fine structural appearance of the normal calibre ureter below the obstructive lesion was the same as in normal ureter. Muscle bundles composed of closely packed smooth muscle cells were separated from their neighbours by relatively little intervening connective tissue (Fig. 7). Each smooth muscle cell possessed a sarcoplasm packed with longitudinally orientated myofilaments together with numerous electron dense bodies. Mitochondria were scattered at random throughout the sarcoplasm while scant granular reticulum and Golgi membranes tended to cluster at either pole of the single, elongated nucleus. Rows of caveolae interspersed with electron dense regions were situated near the sarcolemma of each smooth muscle cell. Individual smooth muscle cells were surrounded by a basal lamina except at regions of close approach (Fig. 8) where a gap of 15 nm separated adjacent cell membranes in the absence

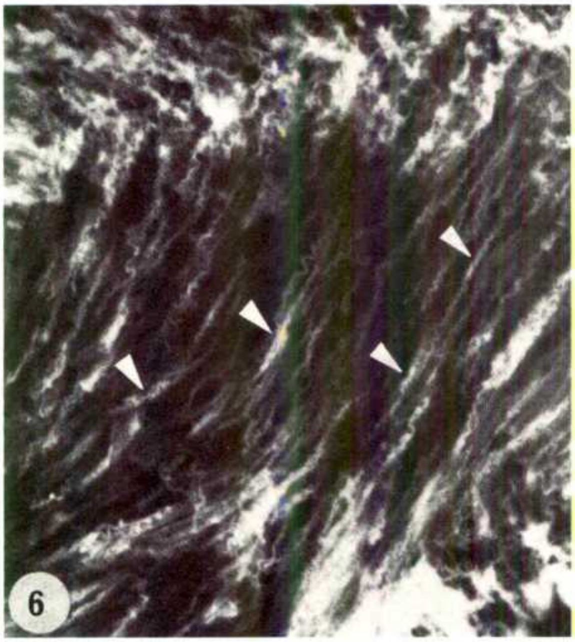

Fig. 6 Sections from dilated portions of the urinary tract show a marked increase in autofluorescent elastic fibres. In this illustration of the renal pelvis in a case of primary obstructive megaureter numerous fibres (arrows) are observed infiltrating between individual smooth muscle cells (×300).

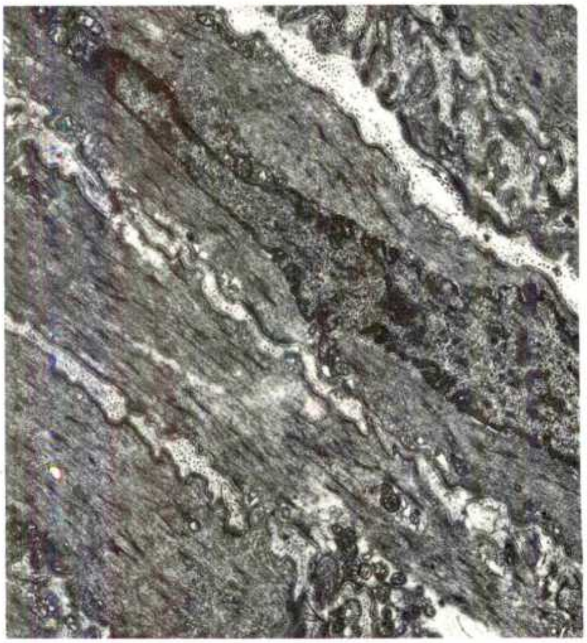

Fig. 7 An electron micrograph of smooth muscle cells from a non-distended segment of ureter. Each cell is packed with myofilaments and is separated from its neighbours by very few connective tissue elements (×6500).

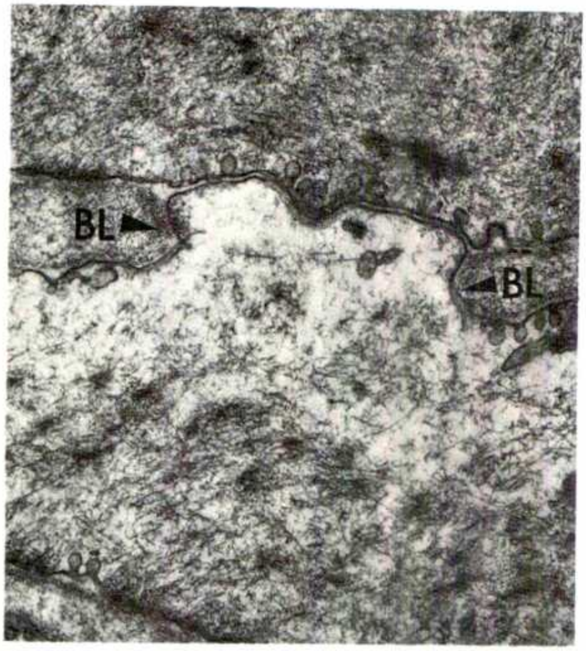

Fig. 8 An electron micrograph of a region of "close approach" between adjacent smooth muscle cells from a non-dilated ureter. A gap of 15 nm separates adjacent cell membranes. The basal lamina, BL, does not extend into the region of "close approach" (×25,500).

of intervening basal lamina material. Such regions were common between adjacent smooth muscle cells within a muscle bundle. The narrow intercellular spaces contained occasional collagen fibres. Elastic fibres were rare. Groups of axons were rare in the proximal ureter and renal pelvis, but were more common in the juxtavesical region where occasional vesicle-filled axonal varicosities were present in close association with adjacent smooth muscle cells.

In the dilated portions of the ureter and renal pelvis the smooth muscle cells were separated from one another by unusually large amounts of connective tissue (Fig. 9). The latter consisted of bundles of randomly orientated collagen fibres together with numerous pale staining elastic fibres (Fig. 10). Many of these fibres possessed dense microfilaments around the periphery which were in continuity with the basal laminae of adjacent smooth muscle cells. Despite the increased amounts of connective tissue, regions of close approach between adjacent smooth muscle cells were as common as in the normal calibre ureter.

In most sections of dilated ureter and renal pelvis marked changes were present in the fine structure of many of the smooth muscle cells.

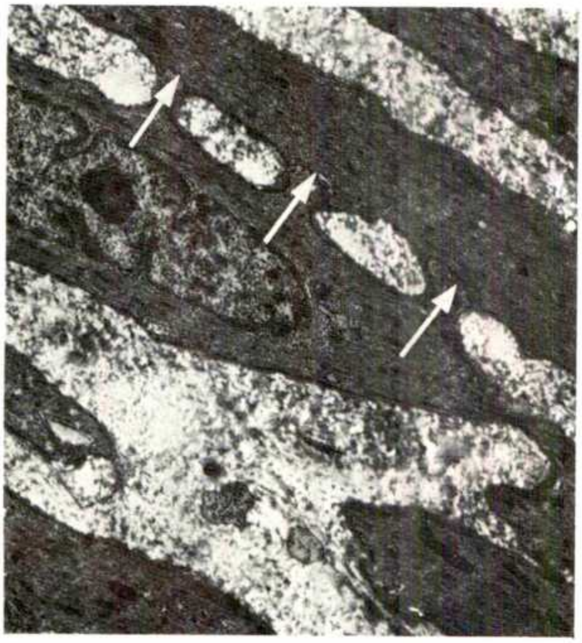

Fig. 9 An electron micrograph from a dilated portion of urinary tract, showing several smooth muscle cells widely separated by connective tissue. Arrows indicate normal regions of close approach between adjacent cells (×7400).

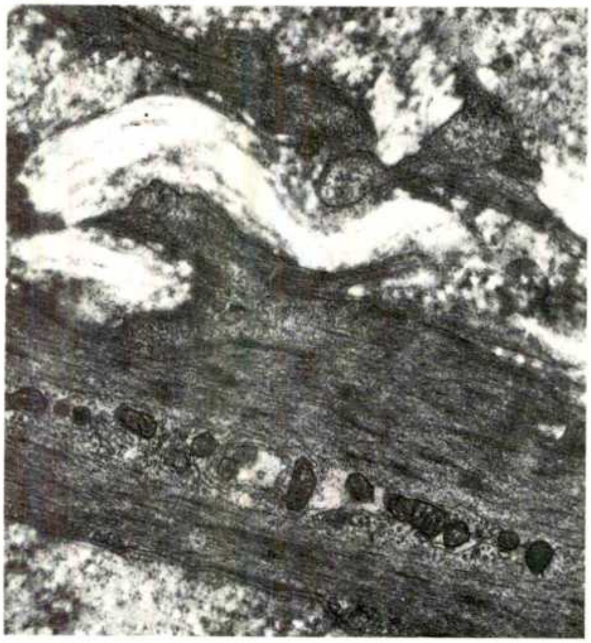

Fig. 10 In this illustration, several pale-staining elastic fibres are in continuity with the basal lamina of an adjacent smooth muscle cell (×14,400).

These alterations in fine structure, whilst similar in all samples from the same dilated ureter and renal pelvis, did vary from 1 patient to another. In some cases the smooth muscle cells showed a considerable increase in their complement of granular reticulum and Golgi membranes, particularly in the perinuclear zone (Fig. 11). In these instances the myofilaments were confined to the periphery and some cells also contained numerous membrane-bound dense bodies and lipid droplets (Fig. 11). In other specimens many of the smooth muscle cells contained a marked increase in electron dense bodies which often formed clusters within the sarcoplasm (Fig. 12).

In all specimens of dilated ureter and renal pelvis the most common fine structural change within the smooth muscle cells was a marked decrease in the complement of myofilaments; such cells often displayed large electron lucent regions within their sarcoplasm and a reduced number of caveolae. Other cells appeared totally devoid of myofilaments and possessed pyknotic nuclei, randomly scattered small mitochondria and very few surface caveolae (Fig. 13).

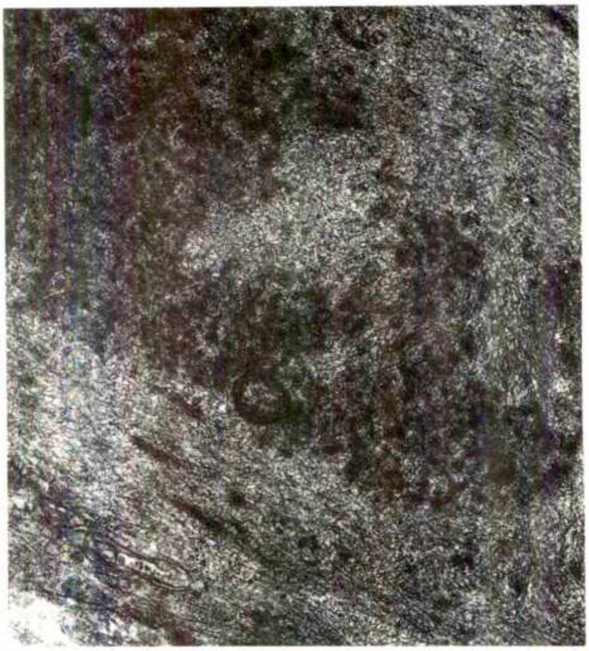

Fig. 12 Clusters of electron dense bodies surrounded by myofilaments occur in this smooth muscle cell from a sample of renal pelvis (×28,800).

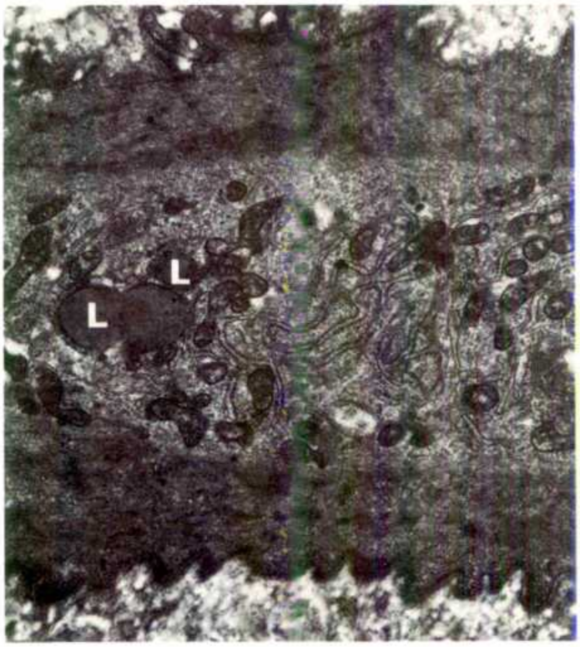

Fig. 11 An electron micrograph of part of a smooth muscle cell from a distended renal pelvis, illustrating extensive granular reticulum and Golgi membranes in the perinuclear zone. Lipid droplets (L) are also present (×11,500).

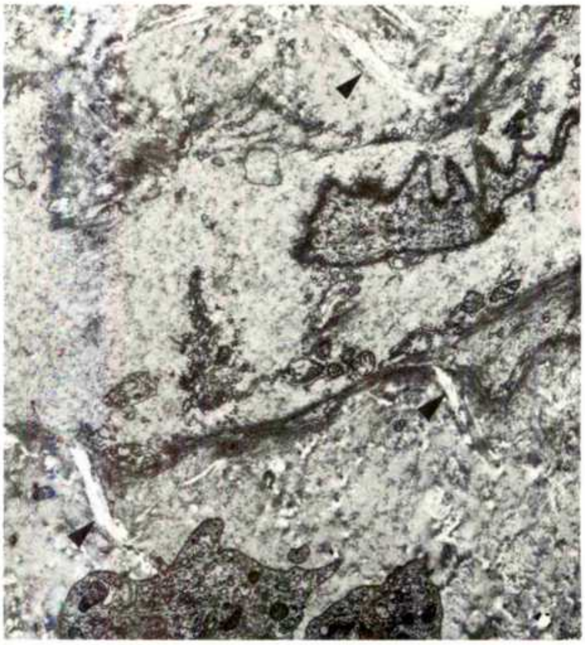

Fig. 13 This electron micrograph illustrates the most commonly observed fine structural change in the smooth muscle cells from distended segments, namely a loss of myofilaments and a reduction in surface caveolae. Arrows indicate numerous elastic fibres closely apposed to the cell surface (×5400).

Discussion

The purpose of this investigation has been to examine and compare the morphology and histochemistry of ureteric smooth muscle in idiopathic hydronephrosis and primary obstructive megaureter. In addition comparisons have been made between the smooth muscle above and below the "narrow" segment. The structural and histochemical changes found in the 2 conditions are essentially similar; only the extent to which the upper urinary tract is dilated differentiates the one from the other. Notley (1971) and Hanna *et al.* (1976) also noted this similarity and—although the details of the structural changes noted in this study vary from their observations—it seems probable that idiopathic hydronephrosis and primary obstructive megaureter have a common underlying cause, acting at different levels in the ureter.

Both Notley (1971, 1972) and Hanna *et al.* (1976) considered the narrow segment of ureter to be of principal importance in the aetiology of the condition, postulating that the marked increase in collagen which they observed acted as an inelastic collar preventing adequate distension of the affected zone during ureteric peristalsis. Although Hanna and co-workers also described morphological changes proximal to this segment, these were thought to arise in response to overdistension and the primary cause was attributed to the "narrowed" ureter. However, the present study has demonstrated excessive amounts of connective tissue extending along the entire length of the distended proximal ureter and renal pelvis. The increase was clearly evident in all cases, including those in which the whole of the distended segment was available for study. This infiltration of connective tissue continued distally as far as the "narrowed" segment where it ceased abruptly. Indeed, the structure of the non-dilated ureter was indistinguishable both histochemically and fine structurally from normal ureter. Neither Notley (1968, 1972) nor Hanna *et al.* (1976) report observations of the dilated proximal ureter or pelvis as remote from the zone of narrowing as in this study. Furthermore their method of study, electron microscopy, limits the size and amount of tissue that can be satisfactorily examined. The combination of these 2 limiting factors compared with the spread of this investigation may account for the difference in the findings.

There is evidence in this investigation that the smooth muscle cells of the dilated ureter above the obstruction may be directly involved in the manufacture of elastin and collagen. Fine fibrils of elastin extend from the basal laminae of these cells and aggregate into large elastic fibres. In addition, the deposition of numerous collagen fibres separating individual smooth muscle cells occurs in the absence of an increase in the fibroblast component of the smooth muscle coat. In some muscle cells a marked reduction in the complement of myofilaments was accompanied by an increase in endoplasmic reticulum, such changes indicating that these cells have increased those subcellular organelles which are believed to be involved in active synthesis, seemingly at the expense of their contractile apparatus. Notley (1971) and Hanna *et al.* (1976) did not comment upon the source of the excessive connective tissue which they observed but the view that smooth muscle is responsible for the manufacture of these components receives support from the work of Ross and Klebanoff (1971) and Gerrity *et al.* (1975). In this context, the marked difference in tissue cholinesterase between the dilated ureter and renal pelvis and the control provides additional evidence of a change in the functional activity of smooth muscle in idiopathic hydronephrosis and primary obstructive megaureter. It may be that this reduction of enzyme in smooth muscle within the wall of the distended segment is directly related to the manufacture of connective tissue by these cells.

In contrast to the findings of Hanna *et al.* (1976), the present study has substantiated the work of Notley (1971) by demonstrating no alteration in the arrangement and fine structure of regions of close approach between adjacent smooth muscle cells. In addition, the structure and distribution of the nerves which supply the upper urinary tract in cases of primary obstructive megaureter and idiopathic hydronephrosis are similar to those in normal ureter. Thus, on morphological evidence, it seems unlikely that the basic aetiology in these conditions is caused either by failure of electrotonic coupling between smooth muscle cells or by abnormalities in the autonomic innervation.

In conclusion, the present study has shown that in primary obstructive megaureter and idiopathic hydronephrosis structural and histochemical changes extend throughout the distended segment of the ureter and renal pelvis. On the basis of these findings it seems unlikely that the pathological conditions are caused by a discrete, inelastic segment of ureter confined to the distal end of the dilated portion. Two alternative hypotheses can be proposed to account for our observations. Firstly, a primary anomaly of ureteric and renal pelvic smooth muscle is present in both conditions which is reflected in fine structural and histochemical changes associated with the manufacture of excessive amounts of connective tissue. On this basis an intrinsic malfunction of muscle cells is the cause for these conditions. Alternatively, the morphological features which occur in the wall of the dilated ureter and renal pelvis could arise as secondary changes in response to distension, the latter due to obstruction from as yet indeterminate causes. In an effort to resolve these possibilities an additional study is currently in progress to determine the histochemistry and morphology of the distended upper urinary tract in cases of obstruction produced by known organic causes.

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Pre-operative Balloon Occlusion of the Renal Artery for Radical Nephrectomy

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Summary—Six of 8 patients with renal tumours were successfully catheterised pre-operatively and the renal artery occluded by a Swan Ganz balloon tipped arterial catheter. At subsequent radical nephrectomy early ligation of the renal vein was readily accomplished and there was noticeable decrease in vascularity and engorgement of the kidney and its tumour.

Radical nephrectomy for tumour may present technical difficulties for the surgeon. Early ligation of the renal vein is essential to prevent tumour emboli. However, ligation of the renal vein, without prior control of the renal artery, results in marked engorgement of the kidney with its tumour, so that most surgeons ligate the renal artery first. The artery lies behind the vein and access may not be easy without undesirable manipulation of the vein. This is particularly true when the tumour is exposed by the commonly used transperitoneal approach or where there are involved lymph nodes in the hilum or para-aortic region.

Pre-operative occlusion of the renal artery allows immediate ligation of the vein and has the additional advantage of greatly reducing the vascularity of the tumour. Percutaneous catheterisation and infarction of the kidney with emboli of Gelfoam, or autologous muscle, is an alternative method of gaining pre-operative control (Almgård *et al.*, 1973; Ben-Menachem *et al.*, 1975; Paster *et al.*, 1975). An inherent risk with embolisation techniques is accidental distal embolus. Marberger and Georgi (1975) have described a method of balloon occlusion of the renal artery in which pre-operative control of the vessel is gained without the use of emboli. We have used this method and report our experience.

Patients and Methods

Eight adults with renal carcinoma have had pre-operative percutaneous balloon catheterisation of the artery of the involved kidney. Seven of the patients underwent nephrectomy via the transperitoneal route and 1 via a supracostal approach.

The patient is transferred from the ward to the radiology department 1 h before surgery. A premedication, which includes an analgesic, is given because pain is common following renal artery occlusion.

Balloon occlusion of the renal artery is accomplished using a 5Fr double lumen balloon tipped Swan Ganz catheter inserted by a percutaneous femoral approach. Introduction is with an 18 gauge arterial needle, a short 0.038 in guide and a 7Fr Desilets-Hoffman percutaneous catheter introducer. The catheter introducer is 2Fr (0.6 mm) larger than the catheter to accommodate the collapsed rubber balloon at the catheter tip. To ensure minimal loss of blood through the 0.6 mm gap between the catheter introducer and the catheter itself, a Tuohy-Borst adaptor, the metal insert replaced with 1½ rubber washers (Fig. 1) is used giving an effective seal. An additional advantage of this modification is that the seal can be varied with ease to allow free manipulation or fixation of the catheter. The catheter is advanced to the origin of the renal artery. The balloon is injected with 0.2 ml of air and the tip

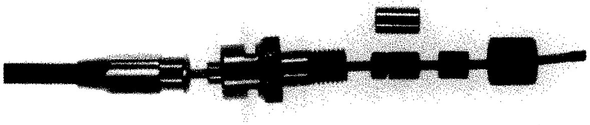

Fig. 1 Tuohy-Borst adaptor, the metal insert replaced with 1½ rubber washers.

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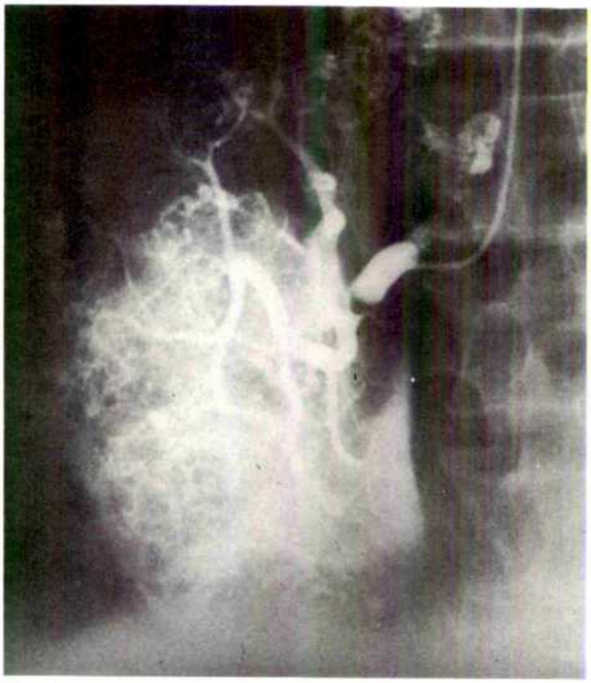

Fig. 2 Balloon occlusion of renal artery. There is a large tumour with pathological circulation. There is no reflux of contrast into the aorta, confirming complete occlusion of the solitary renal artery.

is manoeuvred so that the flow of blood draws the balloon and catheter into the vessels. Occasionally the catheter may be drawn into the wrong vessel; the balloon is then deflated, repositioned and with the tip in place, a small amount of contrast is injected to confirm positioning. The balloon is then inflated to 0.8 ml (maximum size), occluding the artery. A further injection of contrast confirms that the vessel is occluded (there is no reflux into the aorta) and contrast leaves the kidney very slowly (Fig. 2). When the final position is satisfactory the seal is tightened to produce complete haemostasis and the catheter is effectively immobilised, thus holding the position during transfer to the operating theatre. Where there are multiple renal arteries, the artery that passes horizontally to the kidney is catheterised (Figs. 3 and 4). Obliquely running vessels can be readily ligated at operation without disturbing the vein. The occluded artery may not supply the tumour (Fig. 4c).

The patient is then transferred to the operating theatre. Analgesia is increased if necessary. At operation the vascular pedicle is exposed and the vein ligated. The artery is then located and controlled by a ligature while an assistant deflates the balloon and withdraws the catheter. The ligature is then tied, the artery doubly ligated and

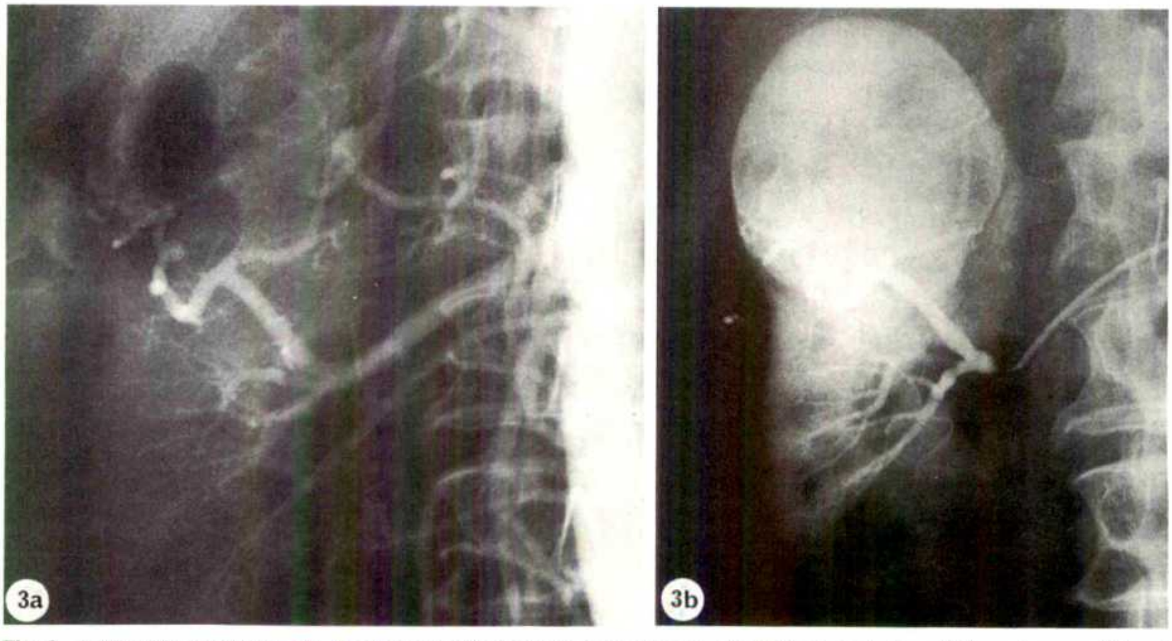

Fig. 3 (a) Double arterial supply to a kidney with an upper pole tumour. (b) Balloon occlusion of the artery supplying the tumour.

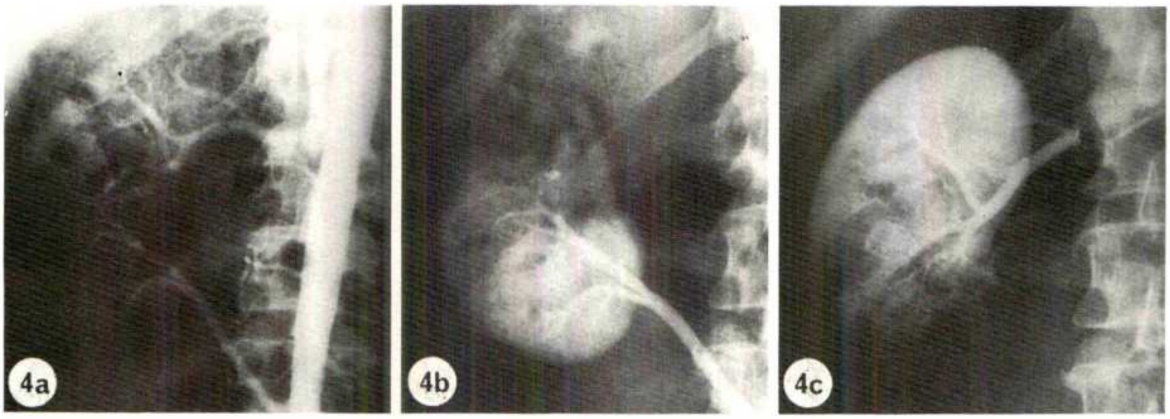

Fig. 4 (a) Double arterial supply to a kidney with a lower pole tumour. (b) Selective arteriogram of the oblique artery supplying the tumour. This vessel was easily accessible for ligation without interference with the renal vein. (c) Balloon occlusion of the horizontal artery to the upper pole.

divided. Where there are double or multiple arteries, the non-catheterised artery is readily ligated as it is not lying behind the vein (Figs. 3 and 4), and as the balloon controls the other artery, the venous return need not be interfered with before the arterial flow is stopped.

Results

It was not possible to catheterise 2 of the 8 patients for technical reasons. In 1, atheroma of the arterial wall prevented insertion of the introducer. In the other, tortuosity of the iliac vessels made it impossible to advance the light, flexible Swan Ganz catheter. However, 6 patients had successful occlusion of the renal artery, including 1 patient in whom it had not been possible to catheterise selectively the renal artery previously. In this patient it was possible to "float" the inflated balloon into the renal artery and a selective film series was obtained immediately preoperatively. In each patient X-rays taken after insertion of the catheter confirmed the arterial occlusion. Due to the consequent reduced blood flow through the kidneys dense nephrograms were obtained (Figs. 3b and 4c).

All 6 patients transferred to theatre after successful catheterisation experienced some loin pain. Two had severe pain requiring morphia. In all patients catheterised, the operative procedure was greatly facilitated and venous ligation was easily accomplished early in the operation.

Discussion

The technique of arterial occlusion with the balloon catheter is simple and can be performed by any radiologist familiar with vessel catheterisation. The procedure may be performed after prior selective renal arteriography. More recently we have established the likely diagnosis with intravenous urogram and ultrasound and then proceeded to Swan Ganz catheterisation confirming the diagnosis and occluding the vessel immediately before surgery. The soft balloon of the catheter will effectively occlude arteries up to a diameter of 1 cm. Bleeding from the 0.6 mm gap between the catheter and the catheter introducer has not been a problem since we incorporated the Tuohy-Borst adaptor. Pre-operative pain which occurs after catheterisation is for a short period and is easily controlled with suitable analgesia. No emboli are used and the danger of accidental emboli into distant vessels is avoided. In the 6 patients successfully catheterised the surgical advantages were rapid ligation of the renal vein and noticeable decrease in vascularity and engorgement of the kidney.

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An Unusual Case of Persistent Renal Collar in a Human Adult Male

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Summary—There are relatively few reports in the literature on accessory renal veins, and particularly that anomaly described as a persistent renal collar.

The present paper describes a case in which a left renal vein is encountered in a human adult, both anterior and posterior to the abdominal aorta, though without a persistent left inferior vena cava.

Material and Description

The cadaver of an adult South African Negro male, dissected routinely in the Anatomy Department, presented the following features (Fig. 1a).

The kidney and renal vessels on the right, as well as the left kidney and renal artery were normal in size, position and relations. The left renal vein however, was anomalous in that it was represented by 2 channels, 1 passing anterior to, and 1 posterior to, the aorta (Figs. 1a, b), thus forming a complete venous ring around the aorta. The renal vein emerging from the hilus of the kidney was single and split soon after emergence into a smaller vessel, posterior to the aorta and a larger channel, passing anteriorly. The 2 channels entered the inferior vena cava without reuniting, the posterior vessel entering at a more caudal level than the anterior one.

Discussion

The condition described here represents the unusual persistence of a renal venous collar that normally develops during ontogeny (McClure and Butler, 1925). Only 3 cases of renal collar in man are documented in embryology texts in common usage (Gray and Skandalakis, 1972). Mitty (1975) has recently found the same anomaly during angiographic investigation of 3 patients.

During normal embryonic development, a system of embryonic venous anastomoses encircle the aorta at the level of the renal veins and it is persistence of these that lead to a renal collar in the adult.

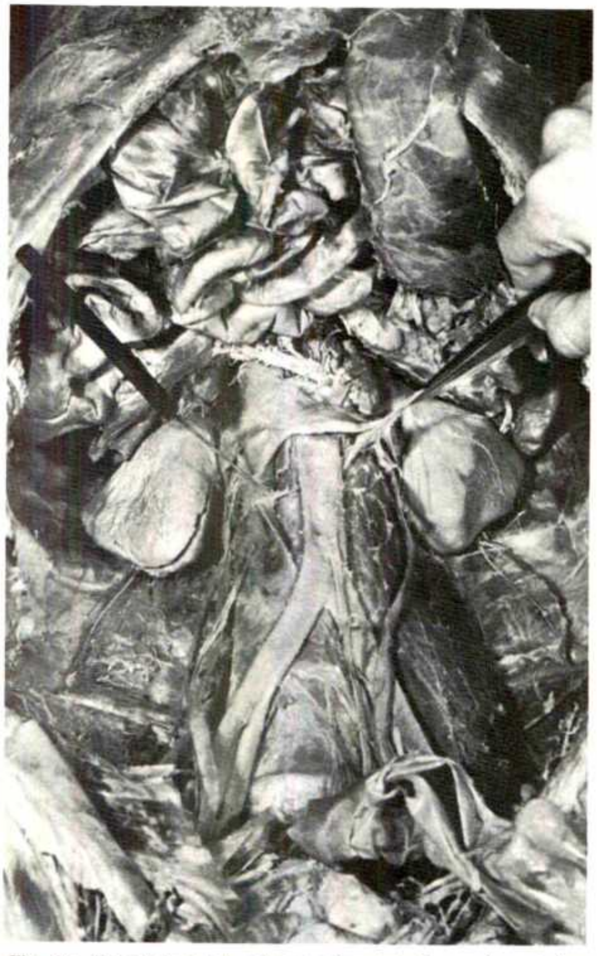

Fig. 1a Two left renal veins passing anterior and posterior to the abdominal aorta.

In a human embryo from approximately 24 days onwards (Hamilton and Mossman, 1972) there appear in succession 3 pairs of veins caudal to the heart. The

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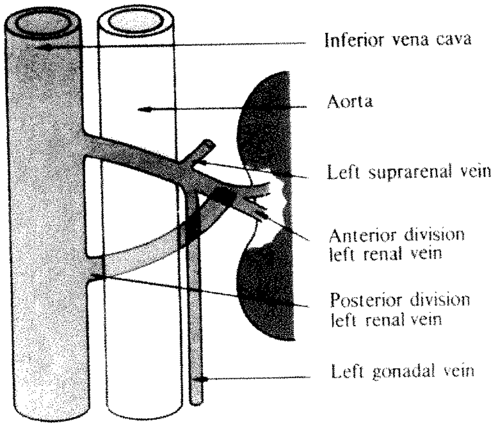
Inferior vena cava
Aorta
Left suprarenal vein
Anterior division left renal vein
Posterior division left renal vein
Left gonadal vein

Fig. 1b Diagrammatic representation of persistent additional left renal vein.

first set to arise are the postcardinals (Fig. 2), which are developed primarily as the vessels of the mesonephroi. The subcardinals appear next and become involved in 2 anastomoses: an intersubcardinal anastomosis across the midline and a subcardinal-posterior cardinal anastomosis on each side (subposterior cardinal anastomosis—Fig. 2). The supracardinal veins are the third set of veins to appear and a subsupracardinal anastomosis is set up on each side (Figs. 2 and 3). A further anastomosis set up across the midline between the 2 supracardinals dorsal to the aorta forms the intersupracardinal anastomosis. Thus a system of anastomoses encircles the aorta at the level of the renal veins. Transformations leading to the final venous plan in the caudal part of the body are complex and are accomplished in the sixth, seventh and eighth weeks of development (McClure and Butler, 1925).

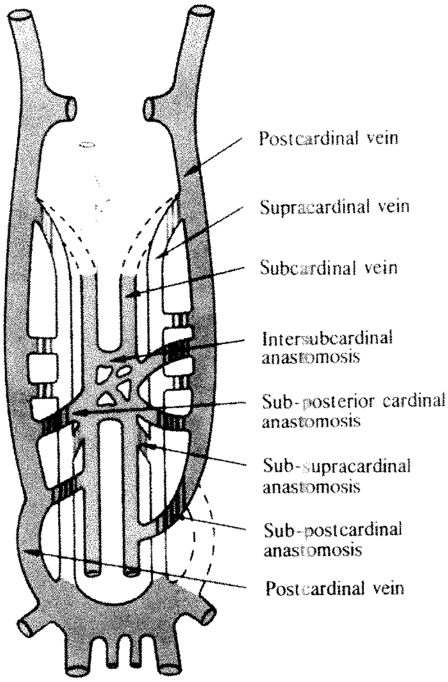
Postcardinal vein
Supracardinal vein
Subcardinal vein
Intersubcardinal anastomosis
Sub-posterior cardinal anastomosis
Sub-supracardinal anastomosis
Sub-postcardinal anastomosis
Postcardinal vein

Fig. 2 Diagrammatic scheme of the primitive veins of the human embryo at 8 weeks of intrauterine life.

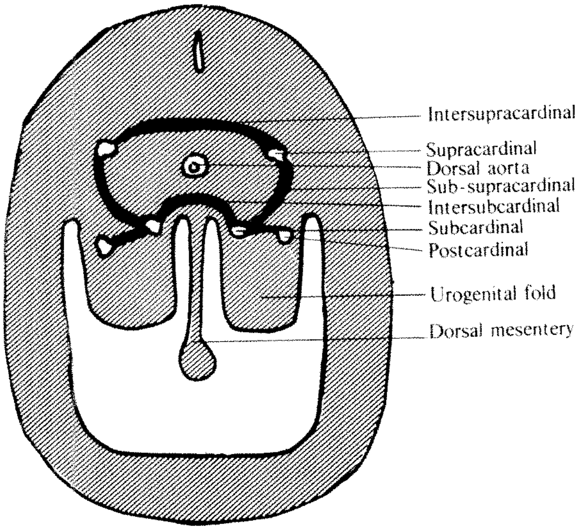

Fig. 3 Diagrammatic representation of a cross-section through an embryo, showing the positions of the cardinal veins and the components of the renal collar.

In man (McClure and Butler, 1925) the ventral component of the renal collar is formed by the intersubcardinal anastomosis and by a small part of the right and left subposterior cardinal anastomosis (Fig. 3). On either side the right and left subsupracardinal anastomosis forms the ring, while dorsally it is completed by the intersupracardinal anastomosis.

In transforming from the embryonic to the adult condition, the renal collar loses its ring-like character and only a portion of it is retained. In man the left renal vein appears to be formed from: (*a*) distally—a new metanephric vein which forms when the metanephros (or adult kidney) has completed its ascent; and (*b*) proximally—by the intersubcardinal anastomosis (McClure and Butler, 1925). The right side of the renal collar is incorporated into the inferior vena cava and the right renal vein is formed from the new metanephric vein on the right.

It appears as though the persistence of the subsupracardinal on the left and more particularly the intersupracardinal has resulted in the anomalous condition described in this paper.

Besides the developmental interest of this case the persistence of a renal venous channel posterior to the aorta is of significance for the vascular surgeon and urologist.

Attention was focused on the retroaortic left renal vein by Brener *et al.* (1974), when as a result of surgical division of an unrecognised limb of the left renal vein during surgery of the abdominal aorta, haemorrhage occurred which resulted in prolonged shock, renal failure and death of the patient. An unknown case of renal collar would be as dangerous, as the surgeon would be lulled into a false sense of security on identifying the anterior component of this anomaly.

Acknowledgements

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The Influence of Wound Drainage on the Infection Rate in Kidney Transplant Patients

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Summary—The frequency of wound infection was studied in 92 patients who had received cadaver kidneys.

Wound drainage was performed in 26 patients and not performed in 66 patients. Wound infection was found in 31% of the wounds with drainage and in 14% of wounds without primary drainage.

The results were compared with the frequency of 34% infected wounds in a previous report where wound drainage was performed routinely.

It is advised that, when possible, wound drainage should be avoided.

The incidence of wound infection after kidney transplantation varies considerably. Sussman and Russell (1972) found wound infections in 9%, Bell *et al.* (1972) in 15% and Kelly *et al.* (1967) in 32%. Kyriakides *et al.* (1975) reported an overall incidence of wound infections in 6.1%, and they demonstrated that recipients of cadaver kidneys had an incidence almost 3 times greater than that found in recipients of kidneys from related donors (3.5%).

Many factors contribute to wound infection, one of which could be wound drainage. In a previous report on 53 kidney transplant patients all wounds were drained and 36 patients had infected drains. Wound infections were demonstrated in 18 (34%) (95% confidence limits 22 to 48) and abscess formation in 9 (17%) (95% confidence limits 8 to 30) (Walter *et al.*, 1975).

The aim of this study was a retrospective evaluation of the incidence of wound infection in kidney transplant patients without routine wound drainage.

Materials and Methods

During the period May 1973 to January 1977 97 patients underwent transplantation with cadaver kidneys. Wound drainage by means of suction drains was avoided when possible. Wound drainage was performed in 26 patients and not performed in 66 patients. The remaining 5 patients had the kidney removed within the first few days.

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Results

In the group with wound drainage, wound infections were demonstrated in 8 patients (31%) (95% confidence limits 14 to 52) and abscesses in 3 patients (12%) (95% confidence limits 2 to 30). As in the previous report many drain tips (18)

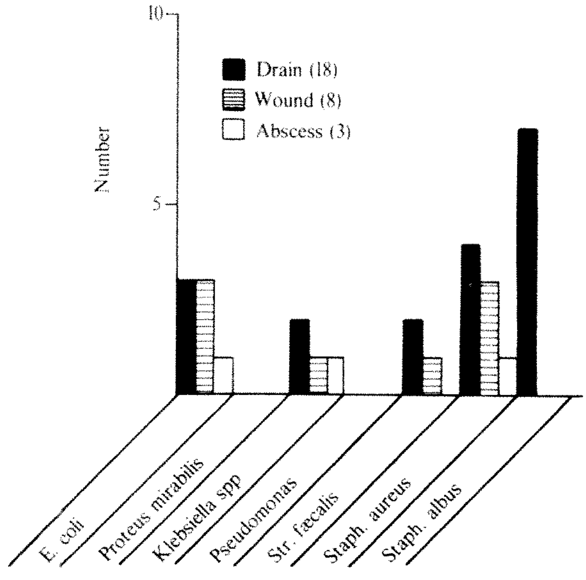

Fig. 1 Bacteria in wound infections in 26 kidney transplant patients with wound drainage.

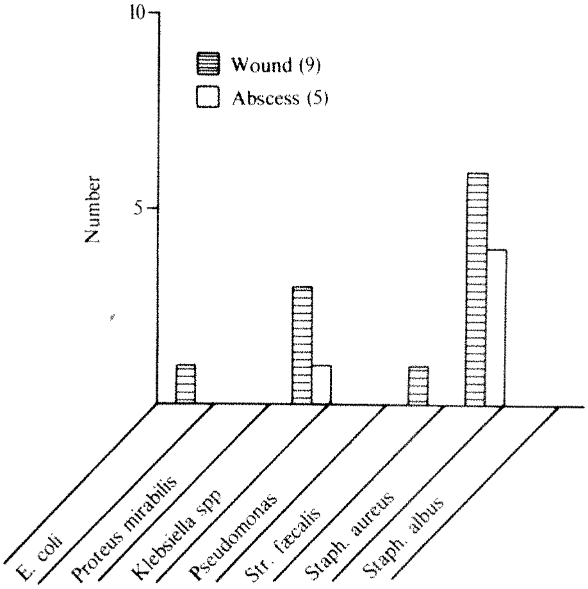

Fig. 2 Bacteria in wound infections in 66 kidney transplant patients without wound drainage. (One patient had mixed flora of pathogens, *E. Coli*, Klebsiella and *Str. faecalis* in the wound.)

were infected; in those infected with *Staph. albus* alone none of the patients (7) subsequently developed wound infections or abscesses (Fig. 1).

In the group without primary drainage, wound infections were demonstrated in 9 patients (14%) (95 confidence limits 6 to 24) and abscess formation in 5 patients (8%) (95% confidence limits 3 to 17) (Fig. 2).

Discussion and Conclusions

Kyriakides *et al.* (1975) showed that unrelated cadaver kidneys, urinary fistulas and wound haematomas were factors predisposing to wound infection in kidney transplant patients. Our previous and this present report show that the frequency of wound infections can be reduced by omitting wound drainage routinely (Walter *et al.*, 1975).

It is important, particularly in patients with kidney transplants, to avoid complications. When possible, the use of drains is therefore to be avoided.

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Delayed Rupture of the Bladder

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Summary—Two cases of delayed rupture of the bladder are presented in which infected urine became extravasated and led to abscess formation with subsequent urinary fistulation.

The management of each case is described and the possible cause discussed.

A suitable radiological investigation of bladder injuries is outlined.

Injuries to the lower urinary tract are usually seen in association with pelvic fractures, the majority as a result of road traffic accidents (Mitchell, 1968). Therefore the possibility that such an injury has occurred should be considered in all patients with pelvic fractures. The types of injury likely to occur are extraperitoneal rupture of the bladder or damage to the proximal urethra. Delayed rupture of the bladder however, is extremely uncommon and may escape recognition. Two such cases are presented which became apparent 2 weeks and 1 month after the initial injury.

Case 1

A 42-year-old policeman was involved in a road traffic accident in which he sustained pelvic injuries with wide diastasis of the pubic symphysis. Urological examination showed no blood at the urethral meatus and his prostate was in a normal position. However he was unable to pass urine and was dull to percussion suprapubically. A small Foley catheter was gently introduced and 300 ml of blood-stained urine was released. Intravenous urography showed a normal upper tract, and retrograde cystography showed an intact bladder with no evidence of extravasation. Two trials without catheter during the first 10 days were unsuccessful. Sixteen days after the injury he developed suprapubic cellulitis with an abscess pointing in the right scrotum, suggesting extravasation of infected urine. A urological opinion was sought.

Cystourethrography showed that the membranous urethra was distorted, but otherwise the urethra was intact. There was a large slough anteriorly; the rest of the bladder was normal. Suprapubic exploration revealed a large haematoma in the retropubic space displacing the bladder upwards and backwards. Although necrotic material could be irrigated from the bladder into this cavity the communication could not be defined. The abscess in the scrotum was incised and this also communicated with the Cave of Retzius. A silastic urethral catheter was inserted and the retropubic space was drained.

Post-operatively a fistula drained through the scrotum, but this dried up within 3 weeks. Five weeks after the operation a cystogram showed there was still a small leak in the region of the bladder neck. The urethral catheter was therefore left *in situ* for a further month. Cystourethroscopy then showed that the bladder had healed and the catheter was removed. Following this he was able to void satisfactorily with good control.

Case 2

A 60-year-old housewife was admitted following a crush injury to the pelvis in which she sustained bilateral fractures to the ischial and pubic rami. She was noted to have haematuria and was initially catheterised. Because of leakage around the catheter this was removed after 1 week, but she developed clot retention and the catheter had to be replaced. An IVP at this time showed an intact bladder. The catheter was again removed 2 weeks later and the patient was then able to void satisfactorily. Four weeks after injury an abscess developed in the left groin which was drained with the release of haematoma and urine. A urethral catheter was replaced but urine continued to drain through a fistula in the left groin in increasing amounts until finally her total urinary output was draining through the fistula.

Cystoscopy at this time showed a perforation on the left side of the bladder. Suprapubic exploration was then carried out when it was apparent that a large area of the anterior and left bladder wall had sloughed. A primary closure was effected. Following this the fistula dried up and the patient was discharged 3 weeks post-operatively. She has had no further urinary problems.

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Comment

These 2 cases presented a similar clinical picture with rupture of the bladder becoming evident 2 and 4 weeks after the initial injury. Both patients had had indwelling catheters with the eventual extravasation of infected urine leading to abscess formation. It is likely that the initial injury to the bladder was a severe contusion and that this in conjunction with pressure from a pelvic haematoma led to secondary sloughing. A retrospective study of bladder injuries reported that contusion was the most frequent injury seen, and that this could be managed conservatively with catheter drainage where indicated (Brosman and Fay, 1973). Contusion was diagnosed on the presence of haematuria and the cystographic appearances.

It is conceivable that the bladder may have been torn initially and that this was disguised by the presence of an indwelling catheter, but both patients had intravenous urography and 1 retrograde cystography which indicated that the bladder was intact. However, intravenous urography may only demonstrate a small proportion of bladder ruptures and retrograde cystography should be considered as the investigation of choice in all suspected cases of bladder injury (Rieser and Nicholas, 1963; Brosman and Fay, 1973). A suitable technique for this examination has been suggested by Cass and Ireland (1973). Two hundred and fifty millilitres of contrast are introduced into the bladder under gravity and an AP X-ray taken. If no extravasation is noted a further 150 ml are added and the X-rays repeated. The bladder is then washed out with normal saline before the final films are taken.

Whether the rupture occurred as a primary or secondary event, the presentation was still delayed with subsequent sloughing of the bladder wall. This possibility should therefore be borne in mind when managing cases of bladder injury.

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A Radioisotope Method of Assessing Uretero-ureteric Reflux

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Summary—A simple radioisotope method of assessing the presence and type of uretero-ureteric reflux in incomplete duplication of the upper urinary tract is described.

The application of the technique in 2 cases is demonstrated.

It is suggested that this simple, non-invasive, non-toxic technique may possess some advantages over conventional methods of evaluating this condition.

Duplication of the upper urinary tract is the commonest congenital abnormality of the genito-urinary system. Most cases are incomplete, the ureters joining before reaching the bladder, and such systems are prone to reflux of urine between the 2 moieties. This may be of the simple "up-and-down" type, where urine is propelled from a dominant moiety to a passive one, or "see-saw" where reflux occurs back and forth between the 2 systems (Tresidder *et al.*, 1970) (Fig. 1). We discuss here 2 patients with uretero-ureteric reflux who have been assessed by a simple, non-invasive isotope technique which appears to be highly useful in this situation.

Method

Routine ^{131}I-hippuran renography was first performed using a simple system of probe detectors. Analogue recordings were made with a 3 sec time constant. This procedure will detect the presence of reflux as activity passes in and out of the field of view of the detectors, the resultant renogram showing characteristic saw-tooth waves. Such a finding in a patient with incomplete duplication and absent vesico-ureteric backflow is indicative of uretero-ureteric reflux.

Following this test, a dynamic gamma camera study was performed using a General Electric Radicamera with Med II computer system. Data were collected and stored in the computer as 15 sec frames over a period of 30 min after the injection of the radiopharmaceutical (^{131}I-hippuran or ^{99m}Technetium-DTPA). Subsequently, regions of interest were defined over the upper and lower moieties of the duplication using a light pen. This allowed renogram curves to be derived for each moiety separately, and from these curves, periods during which activity was markedly different in the 2 moieties were selected. The data were then summed over these periods, and the resultant image used to identify the 2 regions more precisely. The renograms were then recalculated.

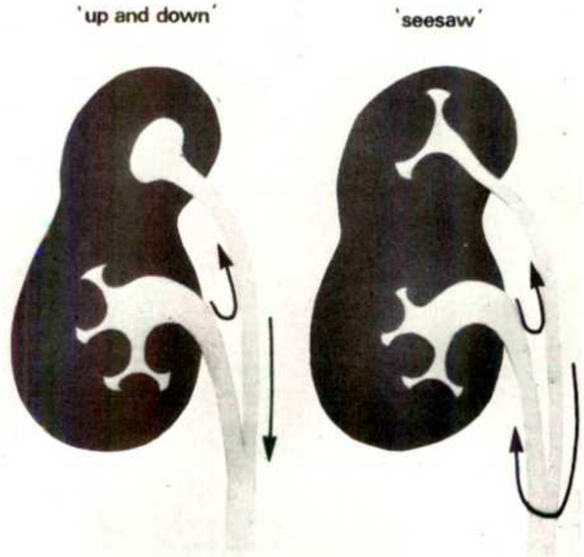

Fig. 1 Uretero-ureteric reflux.

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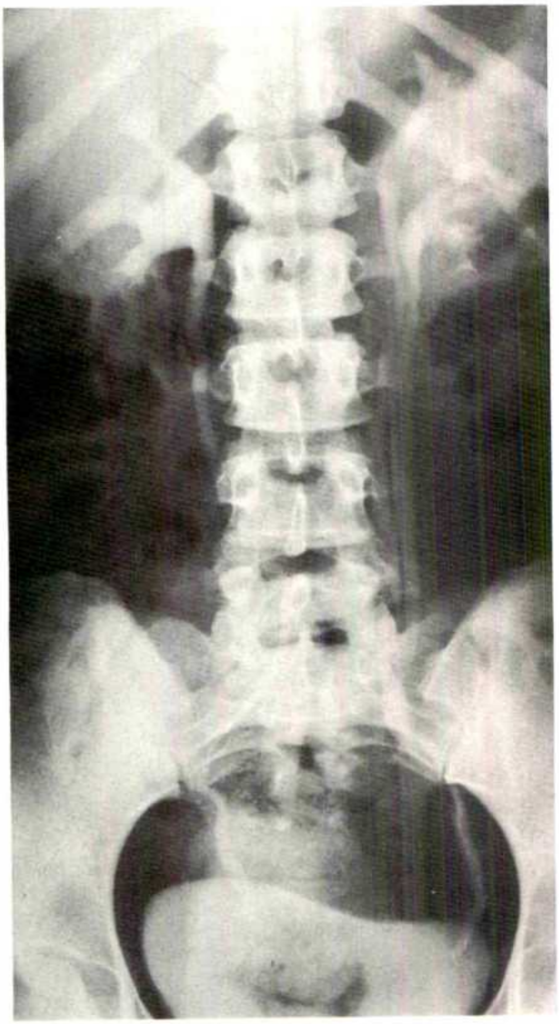

Fig. 2 Excretion urogram from patient with left incomplete duplication of the upper tract (Case 1).

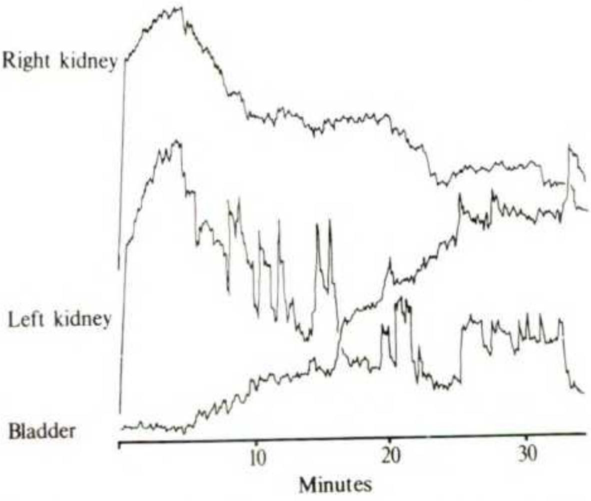

Fig. 3 Initial probe ^{131}I-hippuran renogram from Case 1 showing rapid fluctuations of activity suggestive of reflux.

Case Report 1

A 23-year-old female was referred for investigation after 3 years of intermittent loin pain which was increasing. There were few associated symptoms, although the pain had been previously put down to recurrent pyelonephritis. Excretion urography had shown a normal right upper tract and a duplex system on the left, with ureters joining at about 2 cm above the ischial spine (Fig. 2). Micturating cystourethrography had disclosed no vesico-ureteric reflux. Cystoscopy and retrograde pyelography were essentially normal. Initial probe renography demonstrated the rapid fluctuations of activity in the left kidney suggestive of reflux (Fig. 3). Although the bladder activity increased in steps, there was no sudden decrease in counts, confirming the absence of vesico-ureteric backflow. Figure 4 shows the result of the subsequent gamma camera study using 150 μCi of ^{131}I-hippuran. The computer-derived renograms for the 2 moieties clearly show that activity is see-sawing from 1 moiety to the other and back again. This is illustrated by the 3 scintigrams representing activity summed over the periods 5-6½, 6½-8 and 8-9½ min.

Case Report 2

A 13-year-old female was referred with a long history of recurrent urinary tract infections and left loin pain. Excretion urography had shown a left duplex system with ureters joining at the level of the fifth lumbar vertebra (Fig. 5). Initial renography using the probe system showed the saw-toothed waves characteristic of uretero-ureteric reflux (Fig. 6). Gamma camera studies in this patient using 5 mCi of ^{99m}Tc-DTPA (Diagnostic Isotopes Inc.) showed that reflux was confined to the lower moiety. Excretion from the upper moiety was normal whereas urine was demonstrated to be passing from the lower moiety to the ureteric confluence and back up the same ureter (Fig. 7—see p. 168).

Discussion

Duplication of the upper urinary tract has been reported in 6% of urological cases admitted to hospital (Thompson and Amar, 1958). About three-quarters of these are unilateral and incomplete duplication, with ureters joining some distance above the bladder, is twice as common as the complete form. Such incomplete duplications are prone to uretero-ureteric reflux, and this is more likely the nearer the confluence is to the

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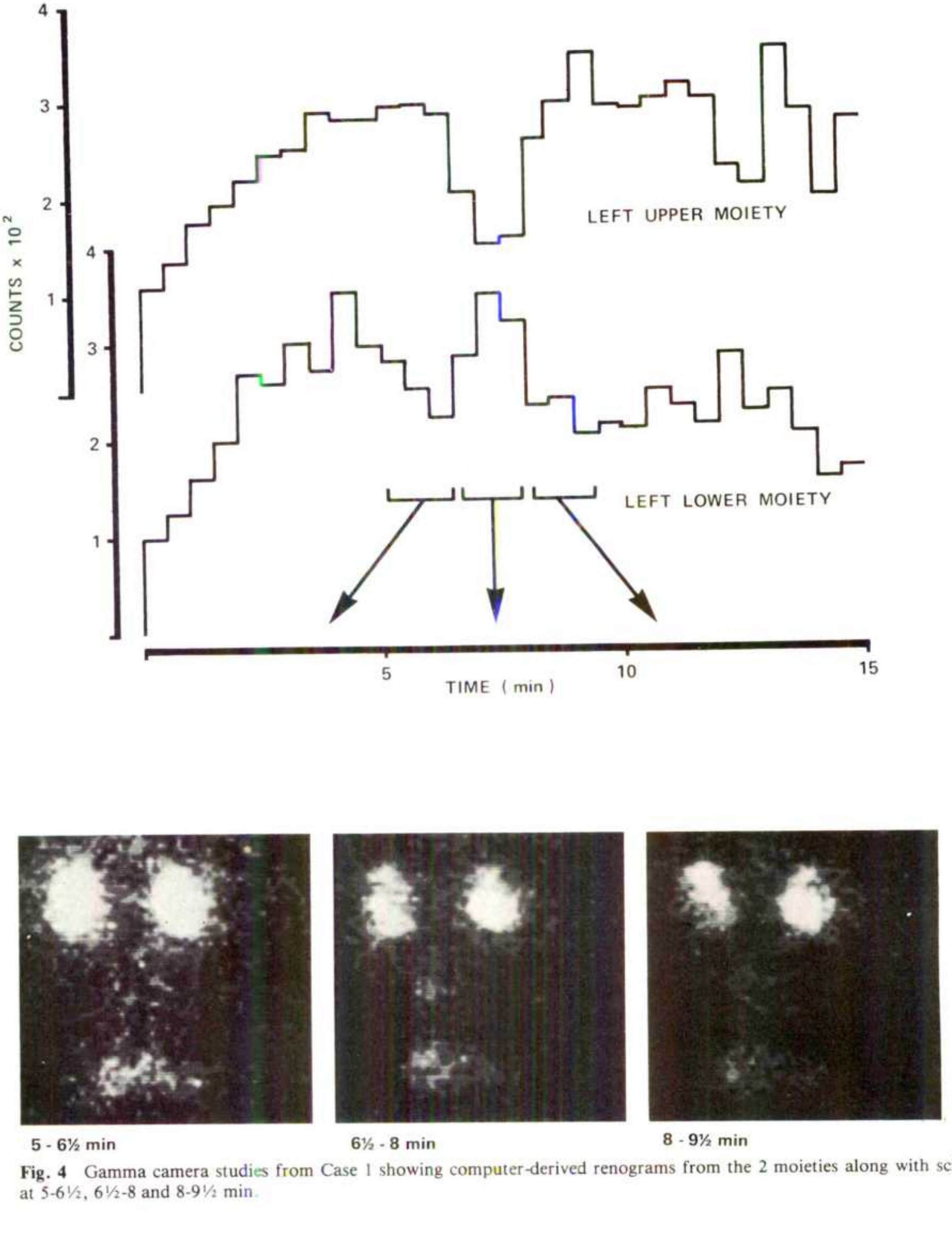
bladder (Lenaghan, 1962; Amar, 1968). Clinicopathological changes secondary to the abnormality occur more often in females than males (Amar and Hutch, 1968). Operation is necessary if complications such as calculus, infection or pain supervene; pain may be caused by the first 2, or by dilatation of the pelvicaliceal system, which can amount to a Dietl's crisis.



5 - 6½ min

6½ - 8 min

8 - 9½ min

Fig. 4 Gamma camera studies from Case 1 showing computer-derived renograms from the 2 moieties along with scintigrams at 5-6½, 6½-8 and 8-9½ min.

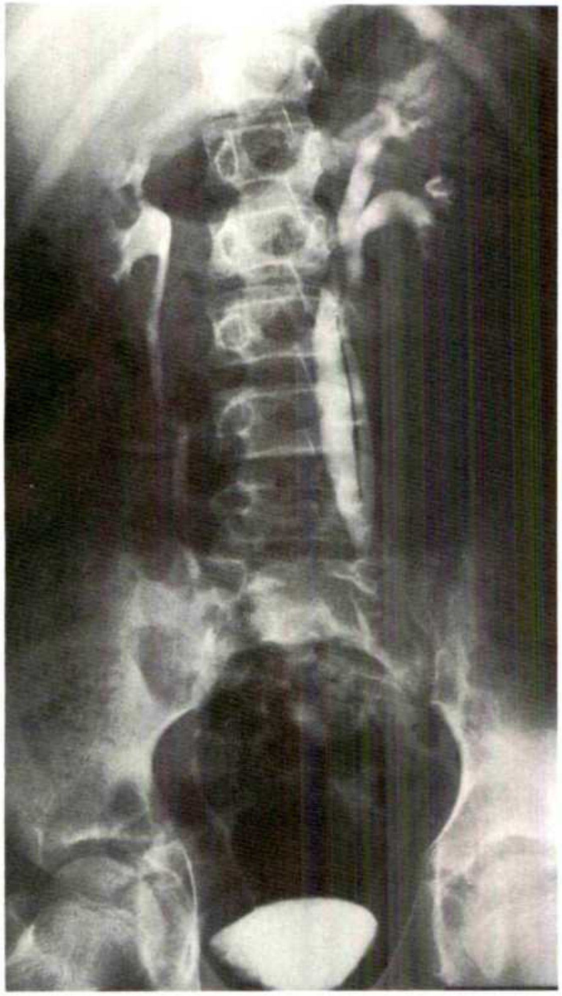


Fig. 5 Excretion urogram from patient with left incomplete duplication of the upper tract (Case 2).

The nature of the corrective surgery depends on the type of reflux and the effect it has had on the renal substance (Tresidder *et al.*, 1970). This assessment has hitherto been dependent on high dose excretion urography with image intensification, which entails a high radiation dose, or on cystoscopy and retrograde pyelography, which is invasive.

The isotope method described here carries a low radiation dose, is simple and quick to perform, is non-invasive, requiring only 2 small intravenous injections and gives a quantitative, functional evaluation of the situation. It will demonstrate the reflux and enable its type, whether up-and-down or see-saw, to be ascertained. Renograms can also be derived for the individual moieties of the duplication. It has been possible to demonstrate reflux in patients using both ^{131}I-hippuran and ^{99m}Tc-DTPA, but the former gives the better result.

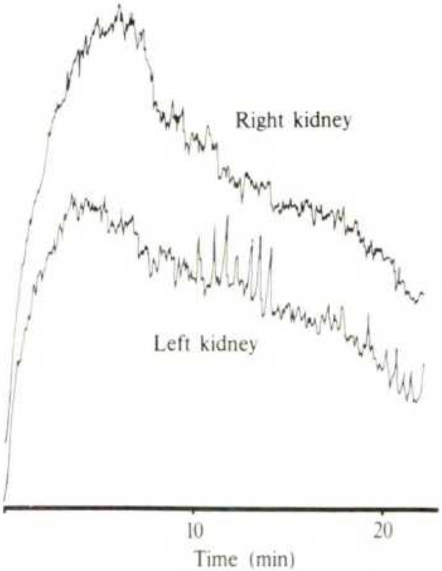


Fig. 6 Initial probe ^{131}I-hippuran renogram from Case 2, again demonstrating saw-tooth waves in the left renogram.

The simplicity of this technique may give it a definite advantage over existing methods of evaluation, although this remains to be proved. Nevertheless, it can be recommended that this isotope assessment be considered in all patients with symptomatic duplication of the upper urinary tract before proceeding to more invasive investigations.

Acknowledgements

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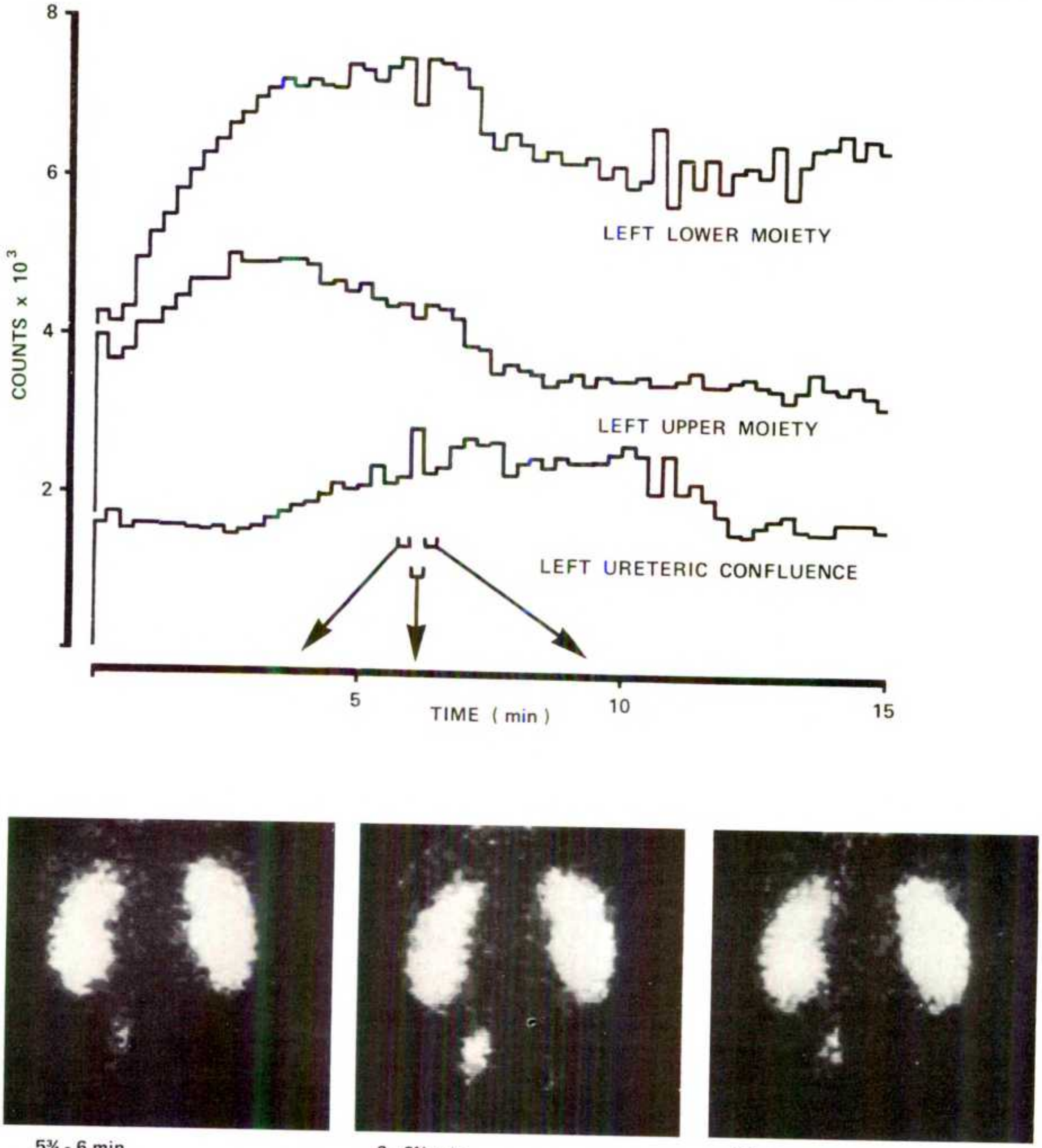

5¾ - 6 min 6 - 6¼ min 6¼ - 6½ min

the corresponding curve from the left ureteric confluence, along with scintigrams at 5¾-6, 6-6¼ and 6¼-6½ min.

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Has Bromocriptine a Place in the Treatment of the Unstable Bladder?

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Summary—A clinical study of bromocriptine in the treatment of 18 patients with an unstable bladder is reported. All patients had previously received drug therapy and/or vesical distension, without success.

Ten of the 18 patients had side-effects, and 2 of these did not complete the study.

Only 2 patients noted moderate improvement in their urinary symptoms.

Bromocriptine appears to be of little value in the treatment of the unstable bladder.

The cystometrogram of patients suffering from urgency, frequency, nocturia, nocturnal enuresis or urge incontinence often reveals uninhibited bladder contractions. Some of this detrusor instability may be a consequence of a urological disease, such as an infra-vesical obstruction in the male (Turner-Warwick *et al.*, 1973) or vesical irritation due to urinary infection. Sometimes the symptoms of detrusor instability may be the result of an overt neurological disorder. However, in most patients urological and neurological examination reveal no abnormality. We think that this primary or idiopathic instability is caused by a hyperactive reflex arc between the receptor organ (the bladder), the sacral micturition centre and the higher central nervous system (Michiels *et al.*, 1976).

Conventional therapeutic modalities aim at influencing this reflex arc at 1 or more levels. Drugs remain the first choice of treatment and the most common are parasympathicolytics and/or β-sympathicomimetics. If these are unsuccessful we advise a smooth muscle relaxant (flavoxate hydrochloride) since in these cases the instability may be due to primary muscular hyperactivity rather than to faulty cholinergic transmission (Delaere *et al.*, 1977). Since some success has been reported using prolonged bladder distension (Dunn *et al.*, 1974) it has been used in patients not responding to drugs; our overall success rate has been 30% (Michiels *et al.*, 1976). Some cases were submitted to a transection of the bladder (Turner-Warwick and Ashken, 1967; Essenhigh and Yeates, 1973), or to a cystolysis, with either limited or no success.

Recently, Farrar and Osborne (1976) reported some success with the use of bromocriptine (2-bromo-α-ergocryptine), a prolactin antagonist, in the management of the unstable bladder. We report our experience with this drug in patients in whom 1 or more of the above mentioned therapies failed to produce a satisfactory improvement.

Patients and Methods

Six male (aged 24 to 67 years) and 12 female (aged 18 to 69 years) patients have been treated with bromocriptine. All patients presented with a history of urgency, frequency, nocturia, urge incontinence and/or nocturnal enuresis.

In the males outflow obstruction as a cause of detrusor instability was excluded. Four patients had a neurological disorder: 1 female had a spastic tetraplegia, 1 male had an upper motor neurone lesion and 2 males had been operated upon for a meningomyelocele. In the remaining 14 patients neurological and urological examination was negative. All patients had previously received drug therapy (propantheline bromide, emepronium bromide, imipramine or flavoxate hydrochloride) without success. Four patients were also treated with prolonged bladder distension and 1 patient underwent a transection of the bladder, without relief of their symptoms.

All patients had undergone a continuous filling cystometrogram (filling rate of 100 ml per min)

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and a pressure/flow analysis and each patient demonstrated unstable detrusor contractions.

Treatment with bromocriptine lasted for 6 weeks. Bromocriptine was administered by slowly increasing the dose in order to avoid the initial side-effects. For the first 3 days each patient received 1 capsule containing 2.5 mg of bromocriptine. Thereafter the dose consisted of 2.5 mg twice a day. The patients were informed of the possible side-effects of the drug. The drug was taken with meals.

Results

Sixteen of the 18 patients completed the treatment. One female stopped the treatment after 7 days and another after 14 days because of distressing lethargy and vomiting. Side-effects in 8 patients were transient and consisted of nausea, headache, lethargy, vomiting, constipation and dizziness (Table 1).

Table 1 Side-effects of Bromocriptine (10 of the 18 Patients)

Side-effects	*No. of patients*
Nausea	8
Vomiting	3
Lethargy	2
Dizziness	2
Constipation	2
Headache	1

Only 2 of the 16 patients who completed the study noted symptomatic improvement, which was attested as moderate (Table 2). Both patients continued to have an unstable pattern on cystometry, though the functional bladder capacity was slightly increased in 1 patient. Only 1 patient of the 2 who benefited agreed to further treatment.

Discussion

Animal experiments have suggested that the pituitary hormone prolactin plays an important part in controlling growth of the prostate (Scott, 1952). Further investigations (Grayhack *et al.*, 1955; Asano, 1965) showed that prolactin potentiated the effect of testosterone on prostate growth in rats. The administration of antiovine prolactin serum could reduce prostatic size in rabbits (Asano *et al.*, 1971). Recently, the effect of bromocriptine as a prolactin antagonist was studied in human benign prostatic hypertrophy (Farrar and Pryor, 1976). It was noted that the symptoms of frequency, urgency, nocturia and urge incontinence, most commonly due to detrusor instability caused by the outflow tract obstruction, improved markedly. However, there was no significant increase in flow rate. Thus the effect of bromocriptine seemed to be due to an effect on the detrusor rather than to relief of the outflow obstruction. This prompted Farrar and Osborne (1976) to carry out a double blind trial to assess its effectiveness in patients with an unstable bladder in the absence of outflow obstruction. Their results were encouraging, in spite of the fact that many of their patients failed to respond to other treatments and only 5 of the 24 patients developed side-effects.

Table 2 Symptoms of 18 Patients with an Unstable Bladder and Results with Bromocriptine

Symptoms	*No. of patients*	*Moderate improvement on bromocriptine*
Urgency	15	1
Frequency	15	2
Urge incontinence	14	2
Nocturnal enuresis	13	1
Nocturia	10	0

The results of our study are disappointing. There was a moderate improvement in only 2 of the 16 patients who completed the trial. In view of these results and also the incidence of serious side-effects, we have stopped using the drug. It may be relevant that our patients with detrusor instability consisted of a selected group not responding to other forms of treatment such as drugs and prolonged bladder distension.

It is known that bromocriptine, a semi-synthetic ergot alkaloid, inhibits prolactin secretion (Pasteels *et al.*, 1971). It use in the treatment of hyperprolactinaemic amenorrhoea and in the inhibition of puerperal lactation is well known. The properties of bromocriptine as a long acting central dopamine receptor stimulant (Corrodi *et al.*, 1973; Thorner, 1975) are probably the basis of its action in Parkinsonism.

The possible effect of bromocriptine on the unstable bladder might be due to a stimulating effect on the central nervous system. However, an antagonistic action of acetylcholine such as demonstrated by Janssen and Jageneau (1957), where bromocriptine reduced gastro-intestinal propulsion, suggests a different mechanism.

It is concluded that, in spite of the possible hypothetical effect of bromocriptine on bladder function, this drug appears to be of little value in the treatment of the unstable bladder.

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Bone Scanning and Plasma Phosphatases in Carcinoma of the Prostate

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Summary—Bone scanning with ^{99m}Tc-Sn-HEDP, radiographic skeletal survey and determination of plasma acid and alkaline phosphatase values were carried out in a consecutive series of 90 untreated patients with carcinoma of the prostate.

^{99m}Tc-Sn-HEDP provided satisfactory bone imaging and was convenient in use.

The addition of bone scanning to radiographic survey increases the detection rate of skeletal metatases by 16%.

Radiography increases the accuracy of bone scanning by identifying false positive scans due to benign disease and false negative scans when there are diffuse symmetrical bony metastases.

The plasma phosphatases alone are less accurate staging tests. The acid phosphatase data support the validity of scan positive—X-ray negative findings. Bone scan abnormalities due to secondary deposits usually precede elevation of plasma alkaline phosphatase.

The role of bone scanning for the detection of skeletal metastases in carcinoma of the prostate has now been well established (Roy *et al.*, 1971; Shearer *et al.*, 1974; Lentle *et al.*, 1974). The isotopes of strontium (Robinson and Constable, 1973) are no longer used because of their physical characteristics (Merrick, 1975) and although Fluorine-18 is at least the equal of any currently available agent, the short half-life restricts its usefulness. The development of technetium-labelled bone-seeking phosphate complexes (Subramanian and McAfee, 1971) has been a significant advance and has made good quality bone scanning widely available. The optimum phosphate complex for bone imaging continues to be a matter for discussion. Hydroxyethylidine diphosphonate (HEDP) has been widely used because unlike the long-chain poly-phosphate complexes, HEDP is a stable compound which does not undergo hydrolysis *in vivo*. Commercially available preparations contain stannous chloride as a reducing agent to convert ^{99m}Tc-pertechnetate to ^{99m}Tc-Technetium. This latter reaction is essential to ensure complexing of technetium to the phosphate component.

The use of plasma acid and alkaline phosphatase determinations in staging has limitations because of the number of false negative and false positive results (Nesbit and Baum, 1951). The present study has provided the opportunity of examining the role of phosphatases, scanning and conventional radiography in the detection of skeletal metastases.

Patients and Materials

Ninety consecutive untreated patients with histologically proven carcinoma of the prostate have undergone bone scanning with ^{99m}Tc-Sn-HEDP and conventional radiographic skeletal survey. Commercially available HEDP (Osteoscan) was used. It was supplied in a sterile ampoule containing 5.9 mg of HEDP and 0.16 mg of stannous chloride which provided sufficient material for up to 5 examinations. Five millilitres of sterile pyrogen free ^{99m}Tc-pertechnetate (Radio-Chemical Centre, Amersham) of sufficient activity to provide 10 mCi for each dose was added within 1 h of intravenous injection. Bone scanning was performed 3 to 4 h after injection using either a Mark III Nuclear Enterprises Gamma Camera or an Ohio Nuclear dual probe rectilinear scanner.

Skeletal survey and bone scanning were usually performed on the same day but always within 2 weeks of one another and before the institution of therapy. The radiographic survey comprised

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examination of the chest, pelvis, lumbar and dorsal spine.

The scans and radiographs were first reported independently and then reviewed jointly by a clinician, a physicist and a radiologist. The material was then classified as Scan Negative/X-ray Negative (Group A), Scan Positive/X-ray Negative (Group B) and Scan Positive/X-ray Positive (Group C).

Alkaline phosphatase was estimated at St Peter's/St Paul's Hospitals in 70 patients by a kinetic technique using para-nitro-phenyl phosphate as the substrate and the values were expressed in King-Armstrong units per 100 ml. At Hammersmith Hospital the Technicon SMA auto-analyser technique with the same substrate was used in 20 patients and the values expressed as international units per litre. A conversion factor was derived by analysis of random specimens at both laboratories which demonstrated an almost linear relationship over a wide range of values. All values have been expressed in King-Armstrong units in the tables and figures. In both laboratories total acid phosphatase activity was measured using the standard King-Armstrong technique with phenyl phosphate as the substrate and the prostatic fractions by the tartrate labile method

Results

Of the 90 patients studied, 23 had osteosclerotic deposits on radiographic examination (Table 1). All of these 23 had positive scans (Group C). The scan positive areas correlated well with the radiographic deposits but abnormalities tended to be more extensive on the scans. None of the remaining 56 patients had radiographic evidence of metastases, but 29 had abnormal scans. In 18 of these 29, the scan positive areas corresponded to benign bone disease on the radiographs (Table 2) and have therefore been classified as Scan Negative/X-ray Negative (Group A). The remaining 11 patients have been classified as Scan Positive/X-ray Negative (Group B) and are assumed to have skeletal metastases. The increased detection rate of skeletal metastases by the use of scanning is therefore 11/67 or 16% (Table 1).

Table 1 ^{99m}Tc-Sn-HEDP Scan Compared to Radiographic Survey in 90 Patients on Presentation

90 patients		*X-ray*	
		Positive	*Negative*
		23	67
Tc-Sn-HEDP Scan	Positive	23	11
	Negative	0	56
			16%

Table 2 Scan Findings in Benign Bone Disease

	X-ray	*Corresponding scan abnormality*
Degenerative changes	24	15
Paget's disease	2	2
Bone Island	1	0
Hemi-hypertrophy	1	1
	28	18

Table 3 Relationship of T-category to Skeletal Studies

	Group A Scan Neg./ X-ray Neg.	*Group B Scan Pos./ X-ray Neg.*	*Group C Scan Pos./ X-ray Pos.*	*Total*
T0	8	0	2	10
T1	3	0	0	3
T2	15	0	0	15
T3	24	9	15	48
T4	6	2	6	14
				90

Table 4 Summary of Elevated Acid and Alkaline Phosphatase Findings

	Group A	*Group B*	*Group C*
Total acid phosphatase	13/56 (23%)	7/11 (64%)	18/23 (78%)
Alkaline phosphatase	8/56 (14%)	2/11 (18%)	20/23 (87%)
Acid and/or alkaline phosphatase	21/50 (37%)	7/11 (64%)	23/23 (100%)
Acid and alkaline phosphatase	0/56	1/11 (9%)	14/23 (61%)

The relationship of the T-category to the skeletal studies is summarised in Table 3. There is a preponderance of T3 and T4 tumours in the metastatic groups (Groups B and C) and of the total number of T3 and T4 tumours, 32 of 62 (*i.e.* 52%) had skeletal deposits.

The relationship of the acid phosphatase and alkaline phosphatase values to the skeletal studies is shown in Table 4 and Figures 1 and 2. The mean plasma acid phosphatase (PAP) value in Group A was significantly different from Group B ($P < 0.001$) and Group C ($P < 0.001$). There

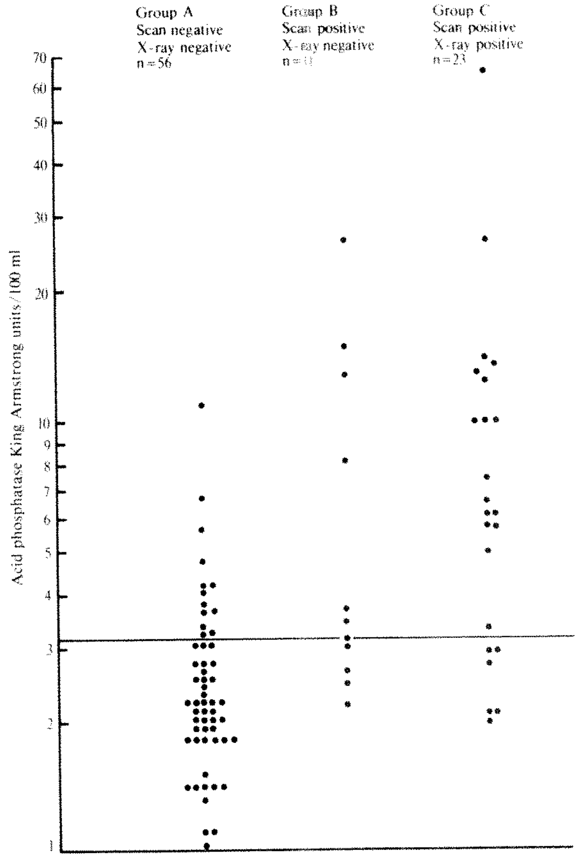

Fig. 1 Relationship of plasma acid phosphatase values to scan and radiographic findings.

was no significant difference in mean PAP values between Group B and Group C (P = 0.2).

In contrast, there was no significant difference in mean alkaline phosphatase values between Group A and Group B (P = 0.2) but Group C was significantly different from both Group A (P < 0.001) and Group B (P = 0.02) (Fig. 2; Table 4).

Discussion

The value of bone scanning in the detection of skeletal metastases has been well established and in reported series of prostatic carcinoma, detectable lesions occur in 10 to 50% of those cases with negative radiographs (Merrick, 1975). A number of factors contribute to this wide variation including the radio-pharmaceutical used, the criteria for selection of patients for scanning, the technique employed, the quality of equipment used, and the criteria of interpretation. Recent experience at Hammersmith Hospital with a large general hospital commitment using ^{18}F revealed a detection rate of 25% (Buck *et al.*, 1975). It may be significant that the majority of patients in the present series presented to urology departments with predominantly local symptoms which may have produced some degree of selection of early disease.

Benign bone diseases are a relatively frequent cause of abnormal scans in this age group and it is mandatory that all scan abnormalities are examined radiographically. Of these, Paget's disease of bone is the most difficult to distinguish from metastatic disease on scanning. The distribution and extent of bony involvement may provide diagnostic clues (Serafini, 1976) but the diagnosis is essentially radiological. The prevalence of Paget's disease in this series (2%) is in close agreement with the reported incidence in the general population (Smith, 1977). Degenerative bone disease is the most frequent benign cause of an abnormal scan. The proximity of such

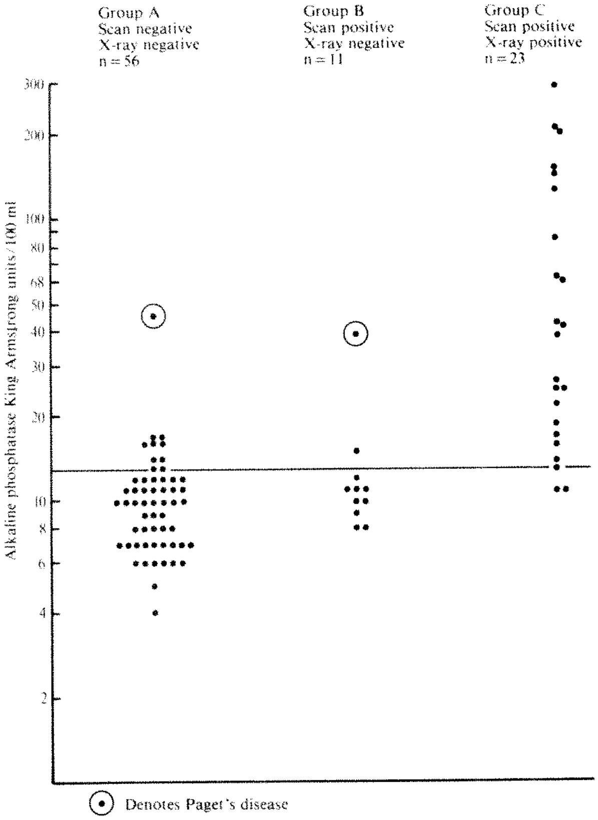

Fig. 2 Relationship of plasma alkaline phosphatase values to scan and radiographic findings.

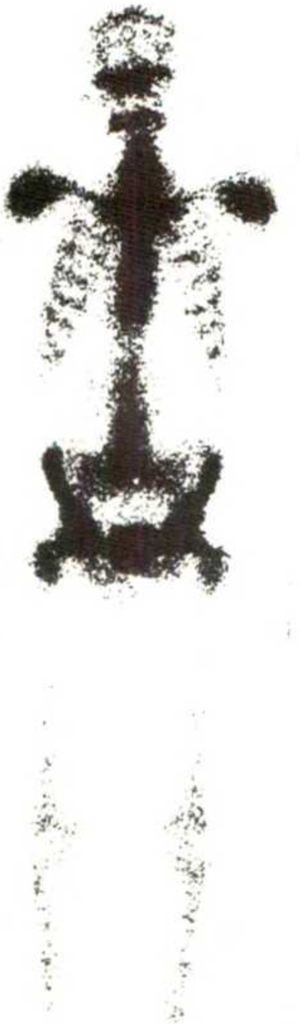

Fig. 3a The "super bone scan" with apparent symmetry. Dense uptake of isotope in central skeleton with reduced or absent uptake in appendicular skeleton and renal areas due to diffuse symmetrical metastases.

abnormal scan findings to joint surfaces is an important diagnostic point and the abnormalities are rarely as well defined as those of secondary deposits. More subtle skeletal changes such as hemi-hypertrophy, osteo-porosis, coxa vara or recent bone fracture may also produce an abnormal scan. The chronological age of such lesions is relevant. Gross radiographic degenerative changes are compatible with a normal scan which apparently reflects the cessation of osteoblastic activity late in its natural history.

The classic radiographic picture of skeletal deposits in prostatic carcinoma is of multiple well-defined osteosclerotic areas of asymmetrical distribution where the scan findings are usually unequivocal. On occasion there may be diffuse and relatively symmetrical involvement of mixed osteoblastic and osteolytic lesions where the scan appearances may cause diagnostic difficulties (Fig. 3a and b). It has long been recognised that lytic lesions are less readily identified by scanning (Charkes *et al.*, 1968). Indeed, current concepts of the pharmacodynamics of radioisotopic bone labels support the view that the presence of newly laid immature bone is the essential prerequisite for increased isotopic uptake (Merrick, 1975). Osmond *et al.* (1975) have coined the term "super bone-scan" in those cases with diffuse skeletal metastases. The skeleton stands out in bold relief with absent or reduced renal uptake which should suggest the possibility of extensive involvement.

Our current policy is to perform a combined isotopic and radiographic survey in view of the risks of false positive and false negative interpretations. Bone scanning and radiographic survey are best regarded as complementary investigations which are carried out when a histological diagnosis of prostatic carcinoma has been made. If either is to be used as an initial screening investigation, it is best that the radiographic

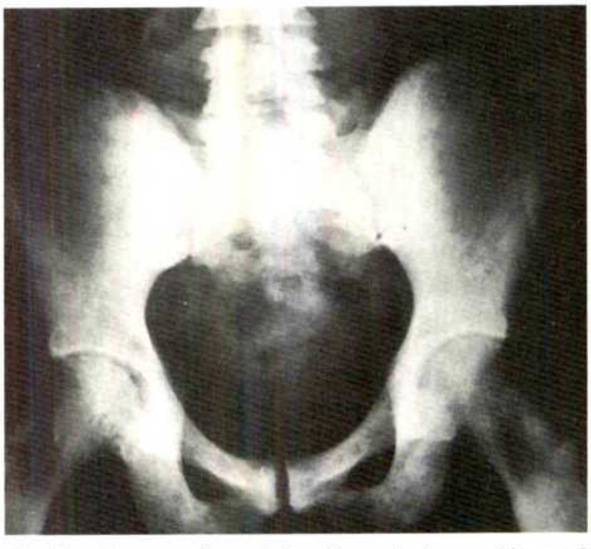

Fig. 3b Corresponding pelvic radiograph shows evidence of widespread metastases.

survey be so used and bone scanning reserved for those with negative findings. This policy minimises the risks of false negative scan findings due to diffuse symmetrical deposits or the effects of treatment (Charkes *et al.*, 1966).

It has long been recognised that plasma acid phosphatase levels are a poor guide to tumour stage (Nesbit and Baum, 1951). It might be supposed that raised values reflect extra-prostatic dissemination or, alternatively, increased metabolic activity in the neoplastic prostatic cell. These explanations are not mutually exclusive. The facts most closely fit the latter with the proviso that a number of tumours may not produce acid phosphatase to any extent perhaps associated with de-differentiation and anaplasia. An elevated plasma level may then be considered as an expression of metabolic activity and total tumour mass. Its particular value in clinical practice lies not in staging but in monitoring response to treatment. Raised PAP levels in 23% of Group A may reflect either a large prostatic primary or soft tissue metastases. The possibility of micro-metastases in bone, not identifiable by scanning, is unlikely since early scan or radiographic conversion in those cases is rare in our experience, and this experience has been confirmed (Buck *et al.*, 1975). The PAP values are significantly higher in Groups B and C but do not differ significantly from one another. This we believe provides good support for the acceptance of Scan Positive/X-ray Negative findings as evidence of skeletal metastases.

The alkaline phosphatase data are of considerable interest. Human plasma alkaline phosphatase is derived from the skeleton, the hepato-biliary system, the intestine and the placenta (Posen, 1967) and it is clearly essential to exclude other causes for elevated values. In practice, the 2 most common conditions are Paget's disease of bone and liver disease. Minor elevations of alkaline phosphatase to the order of 18 King-Armstrong units do not have sinister significance in Group I (see Fig. 2) and there is no evidence that these cases develop skeletal metastases early in the follow-up. Patients with values above this level on presentation in whom Paget's disease has been excluded are likely to have radiographic evidence of metastases. Bone scan abnormalities precede elevation of alkaline phosphatase which is in agreement with the observations of De Nardo *et al.* (1972). Bone scanning, alkaline phosphatase and osteosclerotic changes on radiographic survey may thus be considered as expressions of osteoblastic activity in descending order of sensitivity.

It has been concluded from this study that bone scanning remains the basis of M-category determination in carcinoma of the prostate and provides information over and above that obtained by radiographic survey and plasma phosphatase determinations. Scanning should preferably be performed together with radiography. Of the 28 patients with T0, T1 or T2 classification, only 2 had skeletal metastases and both were T0 tumours. Fifty per cent of the T3 and T4 have skeletal metastases; 50% of the remainder have nodal deposits (O'Donoghue *et al.*, 1976) and so 25% of T3 and T4 lesions are localised tumours and may be curable by radiotherapy.

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The Role of Bone Scanning in the Assessment of Prostatic Carcinoma

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Summary—Fifty new cases of carcinoma of the prostate were assessed prior to treatment to determine the incidence of bony metastases. The radioisotope bone scan was the most sensitive method of detecting metastases and of localising them. It was twice as accurate as the serum acid phosphatase estimation. Skeletal X-rays were the least accurate method. Forty-six per cent of patients had abnormal bone scans at presentation.

The histological grade of the tumour correlated well with the bone scan. The higher the grade, the more likely was the bone scan to be abnormal. There is need for greater accuracy in detecting metastases, and the bone marrow acid phosphatase estimation, either alone or in conjunction with the bone scan, may provide this accuracy.

Carcinoma of the prostate is the commonest genito-urinary malignancy in the male and accounts for nearly 12% of all male cancer deaths in Australia (*Australian Bureau of Statistics Report*, 1973). The incidence of bony metastases at the time of diagnosis has been reported in 2 recent series as 56% (Buck *et al.*, 1975), and 34% (Lentle *et al.*, 1974). These figures were obtained using radioisotope bone scans, one of the most sensitive methods to date of detecting bony deposits in prostatic carcinoma.

The present prospective study reports our experience with the whole body bone scan in the initial assessment of patients with prostatic carcinoma.

Patients and Methods

Seventy-five new patients with prostatic carcinoma were seen over a period of 3 years. The age range was 52 to 88 (mean 72.4) years. Because some patients came from country areas, only 50 cases could be selected for detailed initial study with a view to long-term follow-up.

The diagnosis was proven in all cases by histological examination of material obtained either at prostatectomy, or by transperineal or transrectal needle biopsy of the prostatic tumour.

Recently we have included cases which our pathologists have called carcinoma *in situ* (cellular atypia of sufficient degree to be called malignant, but without evidence of invasion).

The pretreatment assessment included a full blood count, ESR, serum acid and alkaline phosphatase estimation, full skeletal X-ray survey and whole body bone scan.

The serum acid phosphatase was estimated by either the tartrate-labile method of Kind and King or the formaldehyde-stable method of Gutman and Gutman and the serum alkaline phosphatase by the method of Kind and King (Varley, 1967).

The bone scans were performed using an Ohio Nuclear 54 Rectilinear Scanner with twin 5 in crystal detectors. Anterior and posterior views were obtained using 2:1 minification. The radiopharmaceutical used was either technetium tripolyphosphate or technetium pyrophosphate. The injected dose was 20 mCi. Dose to scan time was not less than 90 min.

The bone scans and skeletal X-rays were interpreted separately, and the results were correlated by an independent observer. We experienced no difficulty in distinguishing benign bone disease from metastases in the bone scans.

Results

Presentation (Fig. 1)

Twenty-two patients (44%) presented with retention of urine. Twenty-seven patients (54%) presented with prostatism; 2 of these also had

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bone pain. One patient presented with bone pain alone.

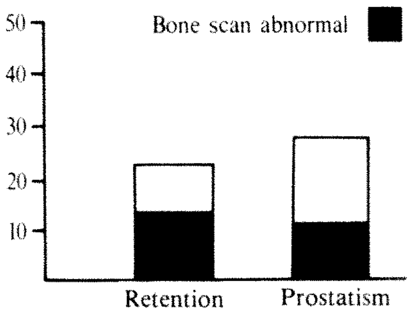

Fig. 1 Method of presentation and bone scan findings.

Blood Count and ESR (Table 1)

Eight patients had a haemoglobin value less than 12 g %. Six of these had an abnormal bone scan.

Fifteen patients had an ESR greater than 25 mm in 1 h. Ten of these had an abnormal bone scan.

Table 1 Comparison of Results of Bone Scans and Blood Tests

		Scan −ve	*Scan +ve*
Haemoglobin	> 12 g %	25	18
	< 12 g %	2	5
ESR	<25 mm/h	22	13
	>25 mm/h	5	10
Acid phos.	normal	25	11
	elevated	2	12
Alk. phos.	normal	26	15
	elevated	1	8

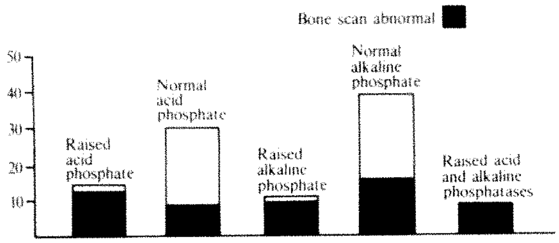

Fig. 2 Acid and alkaline phosphatase results and bone scan findings.

Serum Acid and Alkaline Phosphatase Estimation (Table 1 and Fig. 2)

Fourteen patients had an elevated serum acid phosphatase and 12 of these had an abnormal bone scan. Ten patients had an elevated serum alkaline phosphatase and 9 of these had an abnormal bone scan. Eight patients who had a raised serum acid and alkaline phosphatase all had abnormal bone scans.

Fifty-two per cent of the patients with abnormal scans had raised serum acid phosphatase levels (Table 1).

Table 2 Correlation between Bone Scan and X-ray

	X-rays	
	Metastases	*No metastases*
Bone scan	6	44
	−0	27
	+6	17
	100% scan +ve X-ray +ve	38% scan +ve X-ray −ve

Skeletal X-ray Survey and Bone Scan (Table 2)

Forty-four patients (88%) had normal X-rays; 17 of these (38%) had abnormal bone scans. Six patients (12%) had metastases on X-ray; all of these patients also had abnormal bone scans.

Twenty-three patients (46%) had an abormal bone scan. Twenty-seven patients (64%) had a normal bone scan.

The characteristic pattern seen on the abnormal scan was one of multiple and widespread areas of increased radioisotope uptake. The lumbar spine and pelvis were very commonly involved, and abnormalities became less frequent towards the periphery of the skeleton.

Histology (Table 3, Fig. 3)

Two patients (4%) had "carcinoma *in situ*". Eighteen patients (36%) had well differentiated adenocarcinoma. Fifteen patients (30%) had moderately well differentiated adenocarcinoma. Fifteen patients (30%) had poorly differentiated adenocarcinoma.

Survival

Ten patients have died from metastatic prostatic carcinoma since the study commenced. Two patients had autopsies, confirming the widespread bony metastases.

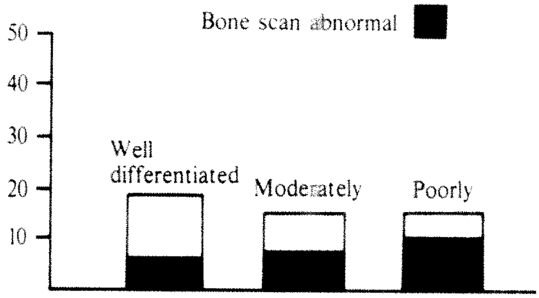

Fig. 3 Tumour histology and bone scan findings.

Table 3 Comparison of Bone Scan Results and Tumour Histology

Histology	*Abnormal scan*	*Normal scan*
Carcinoma *in situ* (2 patients)	0	2
Well-differentiated (18 patients)	6	12
focal (10)	3	7
invasive (8)	3	5
Moderately differentiated (15 patients)	7	8
focal (1)	0	1
invasive (14)	7	7
Poorly differentiated (15 patients)	10	5
invasive (15)		

Discussion

Radioisotope bone scanning is one of the most sensitive methods currently available for the detection of metastases from prostatic carcinoma. The presence of metastases is a contraindication to radical surgery or radiotherapy aimed at eradicating the disease in the prostate gland and the regional lymph nodes. The bone scan has been established as a method of assessing the extent of the disease prior to commencing therapy (Lentle *et al.*, 1974; Bisson *et al.*, 1974). A localised area of increased radioisotope uptake on a bone scan may result from benign bone disease, such as osteoarthritis, osteoporosis, or Paget's disease. Having excluded such possibilities, an abnormal bone scan in a patient with carcinoma of the prostate is diagnostic of metastatic disease. This has been proven in several series, both by bone biopsy of scan-positive areas and by long-term X-ray follow-up of patients who presented with an abnormal bone scan (Buck *et al.*, 1975; Roy *et al.*, 1971). The problem of false negative bone scans has been studied by Gursel *et al.* (1974) who found that half of the patients with normal bone scans had elevated bone marrow acid phosphatase, indicating metastatic disease. A bone scan will show an area of abnormality when a tumour excites an osteoblastic response. De Nardo *et al.* (1972) found that those patients with normal bone scans and metastases on skeletal X-rays all had anaplastic tumours, with osteolytic rather than osteoblastic deposits.

Manipulation of the hormonal environment of the tumour is still the mainstay of treatment in prostatic carcinoma. It would be desirable to assess the response of the primary tumour and its metastases to this treatment, but as yet there is no satisfactory method of doing this. Serial bone scans have been advocated as a means of following the response of the tumour to hormonal therapy. Buck *et al.* (1975) reported 1 patient whose bone scan and X-ray changes reverted to normal after 4 years of treatment. Gursel *et al.* (1974) had 2 patients in whom the bone scan and bone marrow acid phosphatase reverted to normal following orchidectomy.

In our series 46% of the patients had abnormal bone scans on pretreatment assessment. This compares with 56% and 34% in 2 other recent series (Buck *et al.*, 1975; Lentle *et al.*, 1974). The blood count and ESR are of limited value, since many of our patients had intercurrent disease which would disturb these results in any case. The serum acid phosphatase estimation is still a valuable test if the level is elevated but, as seen in this series, only half the patients with abnormal bone scans had an elevated serum acid phosphatase level.

Skeletal X-rays are a very unreliable method of diagnosing metastases. Thirty-eight per cent of our patients with normal X-rays had abnormal bone scans. This figure is comparable with 41% quoted by Lentle *et al.* (1974) who also used a technetium isotope for their scans.

Table 4 Correlation between Tumour Histology and Presentation of Carcinoma of Prostate

Presentation	*Well and moderately-differentiated*	*Poorly-differentiated*
Retention (20)	10	10
Prostatism (27)	23	4

The histological grade of the tumour provides an indication of the likelihood of metastases. However, some patients with tumours which were reported as focal in their prostate glands had abnormal bone scans. In relation to the method of presentation, those patients who had retention of urine showed a higher proportion of abnormal scans and more undifferentiated tumours than those presenting with symptoms of prostatism. Interesting as this observation is, there were insufficient cases for statistical evaluation.

Although the bone scan is a very sensitive method of detecting metastases, several reports have suggested that the estimation of bone marrow acid phosphatase levels may be more accurate than the bone scan (Gursel *et al.*, 1974; Chua *et al.*, 1970).

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The Effect of Routine Digital Examination of the Prostate on Serum Acid Phosphatase

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Summary—Hock and Tessier in 1949 recorded an elevation of serum acid phosphatase levels in 17 out of 20 patients 1 h after prostatic massage. Since that time, it has been widely held and taught that prostatic massage causes a rise in the serum acid phosphatase levels for up to 48 h.

This study was designed to evaluate the effect of prostatic examination on serum acid phosphatase levels, along with the magnitude of laboratory variations and the effects of tourniquet application on blood sampling.

Patients and Methods

The first part of the trial was performed by 3 observers, 2 in the same hospital, the third in another. Each observer admitted a series of 25 male patients to the trial. These were aged 65 and over, consecutive and unselected except that informed consent was required, and patients with indwelling urinary catheters or clinical evidence of carcinoma of the prostate were excluded.

Patients were not fasted prior to blood sampling. From each group, 20 patients chosen at random had blood taken for acid phosphatase estimation immediately before, and at intervals of 30 min, 4 h, 24 h and 48 h after digital rectal examination. The other 5 patients acted as controls—blood was taken at similar time intervals but rectal examination was deferred until after the final blood sample. Each 24 h specimen was divided into 2 parts to detect possible laboratory variation. All specimens were taken without tourniquet pressure except at 48 h when samples were taken concurrently from both arms, 1 with and 1 without tourniquet pressure.

All examinations were performed in the morning. Rectal examination was carried out after evacuation of the bladder. The examination lasted 3 min during which the tone of the anal sphincter was noted, the rectal wall was palpated and the size and consistency of the prostate was noted. Prostatic massage was not performed.

The results of 2 observers (50 subjects) were measured at the University Hospital of Wales by the Auto-Analyser method (Powell and Smith, 1954; Kind and King, 1954). Results are expressed in international units (normal range 2 to 12 iu). The third observer's results were measured in the Department of Medical Biochemistry at Bridgend General Hospital by the micro-analytical method (King, 1951) and expressed in King-Armstrong units (normal range up to 2 King-Armstrong units).

Statistical Methods

Changes in SAP since period 1 were assessed using a paired t-test for each observer's results. In order to overcome the problem of different units, the changes recorded by each observer were standardised by division by an estimate of residual standard deviation from his own results, viz.: the interaction between times and subjects within treatments, based on 138 df. This facilitated combination of the results of the 3 observers (Table 1).

Results

Values obtained in patients undergoing rectal examination by Observer 1 were consistently higher than those under Observer 2. The difference attained statistical significance before examination as well as 30 min and 48 h later, both with and without tourniquet. This suggests variation between patients rather than observer technique. Tourniquet pressure affected neither observed mean levels nor variability.

Thirty minutes after examination SAP had

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Table 1 Mean Levels of Serum Acid Phosphatase

Observer	*Units*	*Group*	*Pre-exam.*	*30 min*	*4 h*	*24 h Duplicated*	*24 h Duplicated*	*48 h*	*48 h with Tourniquet*
1	iu	Rectal Exam	12.8	12.7	11.8	11.8	11.4	13.3	12.1
		Controls	12.4	11.0	9.4	10.6	11.2	9.2	9.2
2	iu	Rectal Exam	10.3	10.4	10.0	10.4	9.9	8.6	8.5
		Controls	10.6	11.2	10.4	8.4	9.2	9.0	8.4
3	King-Armstrong unit	Rectal Exam	1.74	1.69	1.37	1.42	1.52	1.52	1.66
		Controls	1.94	1.92	1.92	2.08	2.14	1.96	2.08

Table 2 Mean Levels of Serum Acid Phosphatase

Time	*1 0 h Pre-exam.*	*2 ½ h*	*3 4 h*	*4 24 h Duplicated*	*5 24 h Duplicated*	*6 48 h*	*7 48 h with Tourniquet*
Group A	0.955	0.875	0.985	1.22	1.115	1.075	0.753
Group B	1.460	1.115	0.985	0.95	1.44	1.395	1.215
Group C	2.314					2.262	

fallen; the fall did not reach statistical significance, and controls showed a similar fall. Values after 4 h, 24 h and 48 h, without tourniquet, showed a significant depression of SAP ($p < 0.001$; $p < 0.005$; $p < 0.04$ respectively) compared to time 1. Controls showed a similar depression which failed to reach significance because of the smaller size of this group. The results of Observer 3 taken in isolation would have sufficed to demonstrate significantly lowered SAP at each of these 3 times; moreover cases examined by Observer 2 had a significantly lower SAP at time 6 than at time 1.

A further 60 men, aged 65 and over, were randomly allocated to 3 groups, A, B and C. Groups A and B were studied by Observers 3 and 4 respectively using the same method as in the first part of the study, but Group C subjects (Observer 3) were bled at 0 h and 48 h in order to assess the effects of blood letting in Groups A and B. Each group contained 20 subjects. The prostate was digitally examined immediately after blood sampling at 0 h in Groups B and C only. Table 2 gives the mean values of the SAP. The SAP in this study was estimated by the Biochemica Test Combination (Fishman and Lerner, 1953; Andersch and Szczypinski, 1947; Richterich *et al.*, 1962).

As in the previous study the SAP fell in both Groups A and B, but the falls were not significant in either Group A or Group B. The falls from 0 to time 6 (48 h) in Groups B and C were practically identical thus there was no evidence that repeated blood letting was responsible for the observed falls.

By the time the second part of the study was commenced, the SAP investigations had been centralised in another laboratory in Cardiff (Table 2), but as the reproducibility of the results fell short of what we felt to be acceptable we have not pooled the total material. However, we feel that the second part of the trial does adequately confirm that repeated blood letting does not influence the serum acid phosphatase levels.

Discussion

An elevation of the serum acid phosphatase has been recorded following massage of the prostate gland (Hock and Tessier, 1949; Bonner *et al.*, 1954; Glenn and Spanel, 1959). Daniel and Van Zyl (1952) reported elevation of SAP levels for up to 24 h in 3 out of 24 patients with benign hypertrophy of prostate following routine clinical palpation of prostate.

Other investigators (Roubicek and Winsten, 1962; Christensen and Mogens, 1972) have found no significant change in serum acid phosphatase levels following digital prostatic examination. There is evidence (Bonner *et al.*, 1954; Dybaker and Jensen, 1958) to suggest that in the presence of prostatic carcinoma, massage of the gland more readily induces a rise in SAP level. Some observers (Hock and Tessier, 1949; Bonner *et al.*, 1954; Glenn and Spanel, 1959) have recorded a rise in serum acid phosphatase in patients with benign prostatic hypertrophy and some subjects without prostatic disease (Bonner *et al.*, 1954; Glenn and Spanel, 1959), but Dybaker and Jensen (1958) and Wiederhorn and Pickens (1973) have failed to show any change on manipulation of the normal or the benign hypertrophied gland. Cases with carcinoma of prostate were not included in our study and because enlargement of the middle lobe is digitally difficult to confirm we did not divide our subjects into those with and those without benign prostatic hypertrophy. Our findings failed to demonstrate a rise of serum acid phosphatase following an adequate prostatic examination.

It has been suggested (Bonner *et al.*, 1954) that some techniques of SAP estimation are more sensitive than others and that these tests will more readily show changes in serum levels following prostatic examinations. The different techniques for SAP estimation used in this study consistently failed to confirm that prostatic examination induced a rise in serum acid phosphatase. There appears to be no justification for the common practice of delaying this investigation on the grounds of a prior clinical prostatic examination.

Conclusion

Routine digital examination of the rectum was performed on 100 elderly male patients. Serum acid phosphatase was estimated in 3 different laboratories on blood taken prior to and at intervals of 30 min, 4 h, 24 h and 48 h after prostatic examination. The same investigation was undertaken on 35 controls who did not undergo rectal examination. We detected a fall, rather than a rise, in serum acid phosphatase.

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The Significance of Bone Marrow Acid Phosphatase in Patients with Prostatic Carcinoma

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Summary—The levels of total and l-tartrate labile acid phosphatase were studied in 49 patients with prostatic carcinoma. The results were compared with the results from a control group.

The acid phosphatase levels from the bone marrow were above the upper normal limit of serum acid phosphatase both in the control group and in patients with prostatic carcinoma. This may be due to acid phosphatase released from blood cells during haemolysis.

There was a positive correlation between serum and bone marrow acid phosphatase levels in patients with prostatic carcinoma. Significantly raised levels of bone marrow acid phosphatase (above the upper limit of the normal range from the control group) were observed only in advanced stage IV patients with significantly increased serum levels.

The levels of bone marrow acid phosphatase gave no supplementary diagnostic information in any of the patients with prostatic carcinoma. Doubt is expressed concerning the hypothesis that raised levels of bone marrow acid phosphatase are diagnostic of early metastases from prostatic carcinoma.

An increased level of acid phosphatase in bone marrow from the posterior iliac spine (BMAP) is claimed to be an early sign of metastatic spread to bone in patients with carcinoma of the prostate (Bruce *et al.*, 1977; Chua *et al.*, 1970; Gursel *et al.*, 1974; Pontes *et al.*, 1975). These authors agree that the determination of bone marrow acid phosphatase can give information which is useful to the clinician.

However, it is well known that raised levels of serum acid phosphatase may be found in patients without prostatic carcinoma (Dow and Whitaker, 1970; Mercer *et al.*, 1977). Others have demonstrated raised levels in patients with haematological disorders (Hoch-Ligeti and Jarsen, 1976; Khan *et al.*, 1977).

In the present study BMAP levels were measured in patients with proven prostatic carcinoma and compared with a control series of patients without carcinoma of the prostate.

Patients and Methods

Seventy-seven samples of bone marrow were taken from the posterior iliac spine in 49 patients with histologically proven prostatic carcinoma. In 19 patients the BMAP determination was repeated during the follow-up period of 24 months. Clinical staging of the disease was performed according to The Veteran Administration Co-operation Urological Research Group (VACURG, 1967).

Most of the patients with stage I-III disease had not received any anti-cancer therapy prior to the bone marrow examination. The majority of stage IV patients had already received anti-androgenic treatment.

The control group consisted of 17 patients (14 males and 3 females) hospitalised for treatment of the following conditions: bladder cancer (10), breast cancer (3), testicular seminoma (2), cerebral tumour (1) and malignant lymphoma (1).

Aspiration of bone marrow with a Kratz sternal needle No. 20 (i.d. 2 mm) produced about 4 ml. Approximately 0.5 to 1.0 ml of the aspirate was placed in a vial for histological examination and the rest was used for the measurement of acid phosphatase. Parallel studies were performed on venous blood. The levels of total and l-tartrate labile acid phosphatase (prostatic acid phosphatase) were determined manually according to the methods of Bessey *et al.* (1946) and Hudson

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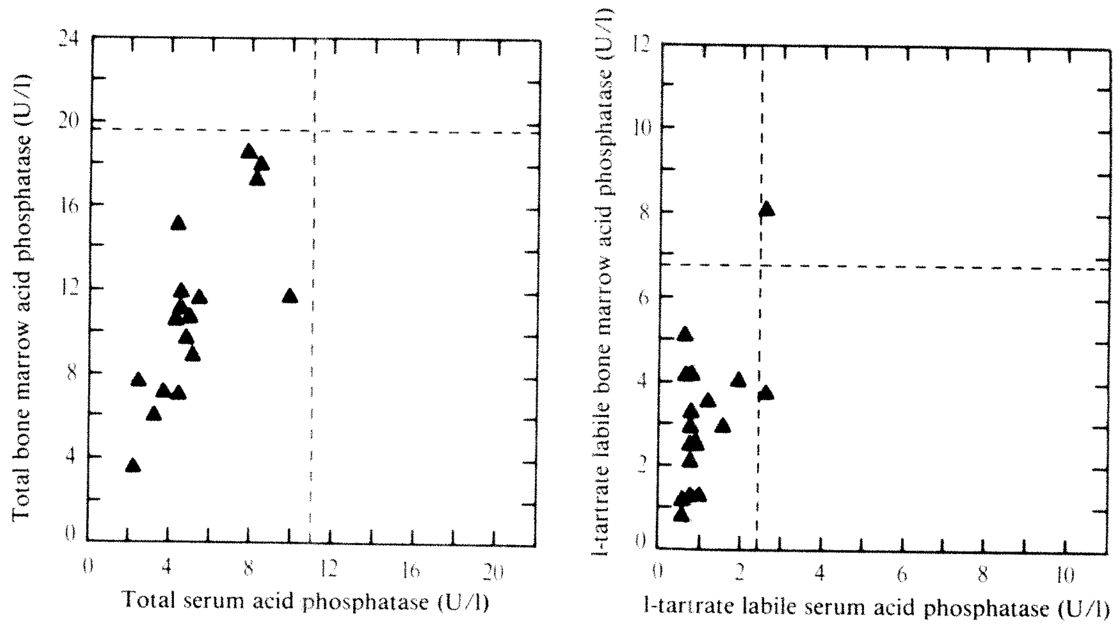

Fig. 1 Acid phosphatase levels in serum and bone marrow in a control group.
------ Upper limit of normal range (mean + 2 × S.D.).

et al. (1947) which are based on the hydrolysis of p-nitrophenyl phosphate buffered with citrate. The upper limit for the serum levels was taken to be 11 U/l for total acid phosphatase and 2.5 U/l for the tartrate labile fraction.

Results

Cytological and histological studies of the bone marrow in patients with prostatic carcinoma revealed normal cellularity in 38 samples. The increased number of lymphocytes suggested chronic lymphocytic leukemia in 2, an increased number of plasma cells suggested myelomatosis in 2 and carcinoma cells in 11. Twenty-four aspirates contained only blood and fat.

The levels of acid phosphatase in serum and bone marrow in the control group are shown in Figure 1. The BMAP levels were generally increased compared to those in serum. Two patients from the control group had marginally raised levels of l-tartrate labile acid phosphatase in the serum. Twelve of the 17 levels for l-tartrate labile BMAP were above 2.5 U/l. The means + 2 standard deviations were 19.6 U/l (total BMAP) and 6.8 U/l (l-tartrate labile BMAP). These values were considered to represent the upper limit of the normal range of BMAP.

The results from patients with prostatic carcinoma are shown in Figure 2. In general, the BMAP levels were increased compared with serum levels. Of 33 patients with localised carcinoma of the prostate (stage I to III), 17 had levels of l-tartrate labile BMAP above 2.5 U/l but below the upper limit of 6.8 U/l established in the control group.

Furthermore, in most cases there was a positive correlation between serum and bone marrow levels in patients with stage IV disease (Fig. 2).

In 11 paired samples the serum total acid phosphatase and total BMAP levels were both increased above the upper control limits. All of these patients had multiple radiographically visible bone metastases. Raised levels of l-tartrate labile acid phosphatase both in serum and bone marrow were observed in 17 paired samples from stage IV patients. On the other hand, 19 paired samples from stage IV patients showed levels of l-tartrate labile serum acid phosphatase and l-tartrate labile BMAP within the limits seen in the control group.

Six patients with stage IV disease had lymph node metastases only. All of these had normal l-tartrate labile acid phosphatase levels in the serum and bone marrow.

Two patients had early metastatic spread to

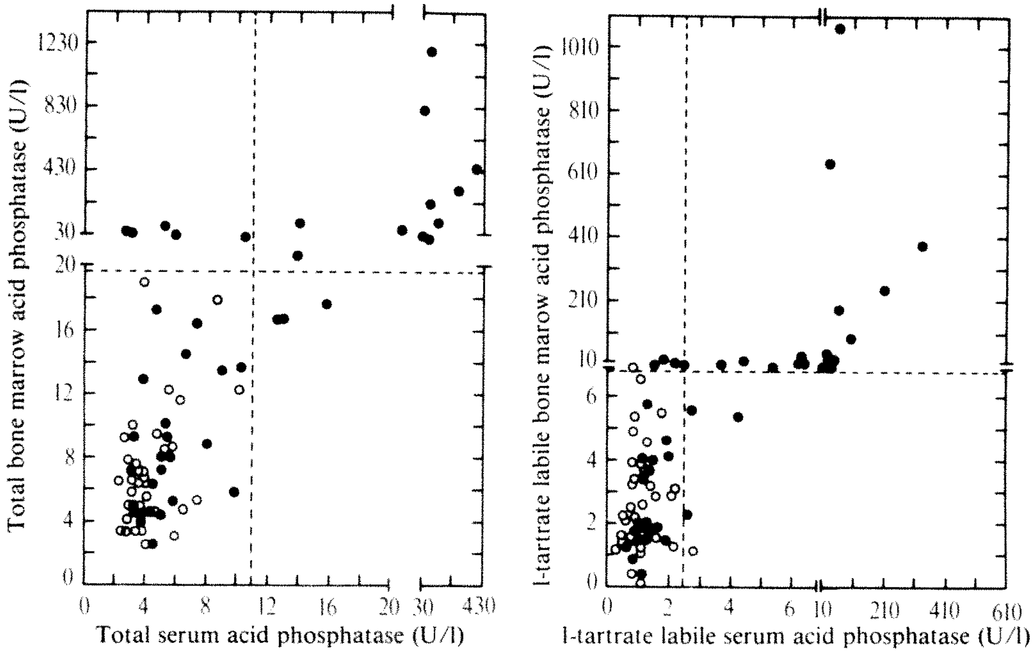

Fig. 2 Acid phosphatase levels in serum and bone marrow in patients with prostatic carcinoma.
○ Localised disease (stage I to III).
● Metastatic disease (stage IV)
- - - - Upper limit of normal range (mean + 2 × S.D.).

bone and analysis of their levels of the acid phosphatase was considered to be of special interest. The first patient had a stage III prostatic carcinoma at the time of diagnosis. The levels of acid phosphatase in serum and bone marrow, measured in 3 separate paired samples, were below the upper limits observed in the control group. The patient was treated by radiotherapy to the primary tumour, but developed a radiographically visible bone metastasis in the second lumbar vertebra after 13 months. No other bone metastases could be detected by X-ray or by bone scanning. No simultaneous increase of the BMAP levels was observed.

In the second patient the only sign of metastatic spread was the detection of malignant cells in the bone marrow aspirate. The simultaneously measured prostatic BMAP was below the upper limit observed in the control group.

Discussion

This study confirms the results of others (Chua *et al.*, 1970; Bruce *et al.*, 1977; Gursel *et al.*, 1974; Pontes *et al.*, 1975) that the levels of BMAP are frequently increased in patients with prostatic carcinoma in comparison to serum levels. This discrepancy between acid phosphatase levels in serum and bone marrow has been explained by the hypothetical existence of barriers "preventing the BMAP from reaching the general circulation" (Chua *et al.*, 1970).

There are 2 interpretations for the observation that prostatic BMAP from the iliac crest may be increased in patients with prostatic carcinoma.

(1) It is claimed that the prostatic acid phosphatase produced in the primary tumour is enriched in the pelvic bones because of venous paravertebral flow and backflow (Gursel *et al.*, 1974). Increasing tumour growth and increasing tumour volume are claimed to be associated with increasing amounts of prostatic acid phosphatase (Reynolds *et al.*, 1973), with the result that raised levels of prostatic BMAP can be expected in patients with advanced primary tumours, even without dissemination of cancer cells to the bone marrow.

(2) It is suggested that prostatic BMAP is produced by prostatic carcinoma cells in the bone marrow secreting prostatic acid phosphatase *in*

situ. If this is true, raised levels of BMAP should be an indication of metastatic spread to the bone marrow. Measurement of BMAP may in this case have diagnostic and therapeutic consequences in the individual patient as claimed by Bruce *et al.* (1977), Gursel *et al.* (1974) and Pontes *et al.* (1975).

Both explanations are consistent with the observation that hormonal treatment decreases the levels of BMAP in patients with prostatic carcinoma (Veenema *et al.*, 1977), as also observed in some of the patients in this study during the follow-up.

Our results, however, do not show higher levels of BMAP in stage III than in stage I, as would be expected if the explanation of Reynolds *et al.* (1973) is correct. Although the number of investigated patients without metastases is small, we did not find any difference between the BMAP levels.

An additional explanation for the raised BMAP levels may be discussed:

Increased levels of l-tartrate labile BMAP may be due to the destruction of blood cells in the bone marrow samples. The acid phosphatase in leukocytes and thrombocytes is, more or less, l-tartrate labile (Mover *et al.*, 1972; Tavassoli and Yelenosky, 1977). The isoenzymes are released from the cells during clotting. It is, in fact, difficult to avoid haemolysis in bone marrow samples. Platelets and leukocytes may be destroyed in haemolysed bone marrow samples, though the degree of cell destruction is usually unknown in the individual sample. The isoenzymes released from the haemolysed blood cells may therefore contribute to the BMAP levels. Furthermore, l-tartrate labile acid phosphatase activity, probably derived from osteoclasts, has been demonstrated in samples from bone (Reif *et al.*, 1973).

The acid phosphatase from these different sources leads one to expect higher levels of l-tartrate labile acid phosphatase in bone marrow samples than in serum, even in patients without prostatic carcinoma.

These theoretical considerations are supported by the results from our control group, which generally showed higher acid phosphatase levels in the bone marrow than in the serum. Our control group supported the suggestions of Hoch-Ligeti and Jarsen (1976) and Khan *et al.* (1977) that it was difficult to define the normal upper limit of BMAP in a control group. Even in women, the BMAP activity was raised above the normal upper limit in serum. Although our control group comprised only 17 samples, it indicates that the normal upper limit of BMAP may be above that defined for serum.

It is claimed that at least 50% of the serum acid phosphatase should be tartrate labile if the result has diagnostic significance in patients with metastatic carcinoma of the prostate (Dow and Whitaker, 1970). This rule should be of particular importance in bone marrow samples because of the increased contribution of non-prostatic l-tartrate labile phosphatase.

Using the upper limits for acid phosphatase levels from our control group, our results suggest that in the majority of patients the determination of BMAP did not give any more information about the stage of the disease than was obtained by the determination of serum acid phosphatase. BMAP levels were only significantly increased in patients with known metastases and seemed—like the serum acid phosphatase—to be loosely correlated with the amount of metastatic tissue.

It must, however, be emphasised that the influence of hormonal treatment prior to BMAP determination in stage IV patients cannot be ruled out. Previous hormone therapy in some of our stage IV patients may have caused a decrease of acid phosphatase in both serum and bone marrow. Six of the patients with stage IV disease had not received any antiandrogenic treatment prior to the BMAP determination. Although distant metastases, even bone metastases, were found in all 6 patients, the l-tartrate labile BMAP levels were within the range observed in the control group.

Our findings are in disagreement with the suggestion that increased activity of l-tartrate labile BMAP may be diagnostic of early metastases in patients with prostatic carcinoma if the BMAP levels are raised above the upper limit for serum levels. A possible reason for this suggestion is that the determination of l-tartrate labile acid phosphatase has, until now, been done by a non-specific method which also measures activity of acid phosphatase of non-prostatic origin.

We agree with Khan *et al.* (1977) that further studies are needed to define the normal level and range of prostatic BMAP in healthy individuals and in patients with non-prostatic disorders. Such studies should be undertaken using a more specific technique for prostatic acid phosphatase determination, for example, radioimmunoassay

(Foti *et al.*, 1975; Skinningsrud and Nustad, 1977).

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Outflow Obstruction in Neuropathic Bladder Dysfunction: The Neuropathic Urethra

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Summary—Urethral pressure profiles were recorded in a series of patients with traumatic lesions of the spinal cord producing vesico-urethral dysfunction. Patients were classified into groups depending upon the relationship of the lesion to the sympathetic outflow to the bladder and urethra from the spinal cord. Using alpha-adrenergic blocking agents, the smooth muscle contribution to the maximum urethral pressure was ascertained in each group and differences in both the configuration of the profile, and the smooth muscle component, were found.

Increases in the maximum urethral pressure in response to a change in posture were also investigated, and the extent of the increase found to vary according to the level of the spinal lesion in respect of the sympathetic outflow, and with the integrity of the sacral cholinergic reflex arcs.

The hypothesis that these changes may be due to urethral "decentralisation supersensitivity" from alterations in circulating catecholamine levels is suggested.

Outflow obstruction at the level of the external sphincter in patients with neuropathic bladder dysfunction was first described by Watkins (1936) in patients with cauda equina lesions. The detrusor is inactive in these cases, and voiding is achieved by straining or Credé expression. While the cause was not clear, the obstruction was shown to be relieved by endoscopic incision of the urethral wall and division of the external sphincter (Ross *et al.*, 1957).

In the presence of good detrusor contractions, as is the case in supra-sacral cord lesions, patients may still be unable to void or have a high residual urine. Emmett (1940) showed that a small bladder neck resection could establish or improve voiding in some of these patients, and this was probably due to relief of inflammatory stenosis. It soon became clear, however, that in some patients in whom detrusor contractions opened the bladder neck, or in whom a small bladder neck resection had been performed, obstruction occurred at the level of the external sphincter. Spasm of the peri-urethral striated muscle was thought to be responsible and this could be relieved by sacral rhizotomy, subarachnoid alcohol block or sometimes by pudendal neurectomy. In view of the high incidence of impotence associated with these procedures, endoscopic division of the region of external sphincter gradually replaced them (Ross *et al.*, 1963, 1967).

Recent studies on cauda equina cases have shown that the urethral obstruction is due to plain muscle activity, and that this can be abolished by alpha-adrenergic blockade (Abel *et al.*, 1974). These observations on the "neuropathic urethra", together with the increasing appreciation of the role of smooth muscle in normal urethral function, stimulated the investigation of the smooth muscle contribution to bladder outflow obstruction at all levels of neurological lesion.

Patients with neuropathic bladder dysfunction, due to traumatic spinal cord lesions, may void more freely when lying flat than when sitting. The investigation of urethral responses was therefore extended to assess the effect of a change of posture upon the maximum urethral pressure, and to see whether this might be of significance in neuropathic outflow obstruction.

Patients and Methods

The patients in this study were selected from those attending the Regional Spinal Injuries Centre in Southport, and were divided into 2 categories, according to whether or not they had

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had previous surgery to the external sphincter. The criteria for inclusion in the study were that the spinal lesions were traumatic in origin, neurologically complete, and showed no recent alteration in the neurological level.

There were 36 patients in the unoperated category (the main series), 33 male and 3 female, with a mean age of 34 years (range 18 to 71). The time following injury varied from 3 months to 28 years although most investigations were performed within the first 12 months following injury. The patients were classified into 4 groups according to the relationship between the upper sensory level and the sympathetic outflow from the spinal cord.

Group 1

Thirteen patients with cervical cord injuries with a neurological sensory level above the upper limit of sympathetic outflow at T1.

Group 2

Eight in whom the level was in the range T1 to T10 inclusive. Thus the lesion involved sympathetic outflow but was above that to the bladder and urethra.

Group 3a

Five patients had an upper sensory level in the range T11 to L2 inclusive, thus implicating the bladder and urethral sympathetic supply. The anal and bulbo-cavernosus reflexes were intact, however, suggesting that the sacral segments were spared, and the parasympathetic supply to the bladder intact.

Group 3b

Seven patients had similar upper neurological levels in the range T11 to L2 inclusive, but with absent anal and bulbo-cavernosus reflexes and therefore presumed damage to both sympathetic and parasympathetic efferents.

Group 4

Three had conus or cauda equina lesions with a damaged parasympathetic supply, but an intact sympathetic outflow.

The second category of patient studied consisted of a group of 6 patients who had all previously had operative division of the external sphincter, but in whom the operation was deemed unsuccessful by virtue of an increasing residual urine or recurrent retention of urine ("Failed DES"). Five of these patients had cervical lesions, the other had a lesion of the mid-thoracic cord.

For comparative purposes, results from a control group of 16 neurologically intact patients, referred with minor urological symptoms and found to have normal voiding dynamics, are included.

Statistical analysis was by the appropriate Students t-test, with a 5% level of significance.

Urethral Pressure Profiles

The urethral pressure profiles were measured using a modification (Harrison and Constable, 1970) of the technique described by Brown and Wickham (1969).

An 8F Porges catheter, perfused with saline at 2.5 ml/min by a Sage constant flow pump, was withdrawn from bladder to external meatus. Pressure changes in the catheter were measured by a side arm connected to a strain gauge transducer. These pressure changes provided the X axis to an X-Y recorder. The Y axis was produced by a catheter position "trombone", to which the profile catheter was fixed during each recording.

Profiles were written using a catheter withdrawal speed of approximately 20 cm/min, and several superimposed recordings made in each patient.

Electromyography

Simultaneous pelvic floor electromyograms were recorded in patients using either a bi-polar needle electrode inserted into the peri-anal muscles, or an anal plug electrode. It was found convenient to use the anal plug in patients with supra-sacral spinal lesions and the needle electrode in patients with a paralysed pelvic floor. The electromyogram was displayed on a San-El ultraviolet recorder together with an alternative recording of the intra-urethral pressures.

Cystometry

Slow filling supine cystometrograms were recorded in every case. The bladder was filled with a 12F transurethral catheter, alongside which was a 1 mm external diameter pressure catheter. Saline at room temperature was infused at a rate of approximately 10 ml/min, and with the symphysis pubis as a zero reference, pressure increases within the bladder continuously recorded.

The Investigation

Recordings were made initially in the supine position with the bladder empty. The effect of a change of posture was then noted by repeating the recordings in the sitting position. A cysto-

Table 1 Maximum Urethral Pressure at Different Levels of Spinal Injury. Mean Values (Standard Error)

Group	*Spinal level*	*No. pts.*	*MUP**	*(SE)*	*Normal*	*(SE)*
1	C4-C8	13	93.6	(11.8)	72.7	(4.4)
2	T1-T10	8	98.5	(11.8)	77.5	(3.5)
3a	T11-L2 BC +ve	5	72.2	(6.8)	68.0	(4.4)
3b	T11-L2 BC −ve	7	53.2	(5.9)	73.3	(4.2)
4	L3-S4	3	48.3	(3.3)	75.0	(9.0)

* MUP = maximum urethral pressure.

Table 2 The Mean Effect of Phentolamine in Each Group

Group	*MUP after phentolamine*	*(SE)*	*Drop (%)*
1	51.0	(6.0)	45
2	44.6	(8.2)	55
3a	63.8	(9.9)	11
3b	29.6	(9.6)	45
4	25.0	(9.6)	48
Normal	54.5	(6.0)	26

metrogram was then recorded, and the urethral pressure profile repeated with the bladder full. The bladder was emptied once more, and the alteration in the profile produced by alpha-adrenergic blockade was measured in each patient. Alpha-adrenergic blockade was produced by a single intravenous injection of 10 mg of phentolamine (Rogitine, Ciba) and recordings made in the supine and sitting position approximately 3 and 5 min after injection. Blood pressure changes were simultaneously measured.

Bladder mucosal anaesthesia using a 30 min instillation of 100 ml of 2% lignocaine was used in 2 patients: 1, in Group 3B, with an L1 lesion, and the other a "Failed DES" case, to determine whether this had any effect on the postural change in urethral pressure.

Results

Maximum Urethral Pressure at Different Levels of Spinal Injury

The results obtained in each of the 4 groups of patients are shown in Table 1.

For comparative purposes, mean values obtained from 16 normal individuals using the same method of study are shown. As there is a negative age correlation in normals (Edwards and Malvern, 1974), the normal values have been corrected to match the spinal injury patients, in respect of age. The higher values found in upper spinal injuries when compared to normal do not show a statistically significant difference ($t = 1.66$ group 1, $t = 1.47$ group 2, $t = 0.6$ group 3a). The values in the cervical and upper thoracic lesions would, however, indicate a tendency for these patients to exhibit higher urethral pressures than normal. Those with lower spinal injuries show statistically significant lower urethral pressures than normal ($p < 0.02$ group 3b). The small number of patients with conus or cauda equina lesions (group 4) excludes statistical analysis.

The Effect of Bladder Filling

The response to bladder filling was variable, and not dependent on the level of neurological injury. Nineteen patients showed a reduction in the maximum urethral pressure when the bladder was filled whilst in 2 cases no change was noted. In 8 patients there was a rise in urethral pressure and this was not always associated with an increase in pelvic floor electromyographic activity. Conversely, a noticeable increase in pelvic floor discharge was sometimes seen in cases with a reduction in the maximum urethral pressure in response to bladder filling.

The Effect of Phentolamine

Alpha-adrenergic blockade invariably reduced the maximum urethral pressure at all levels of spinal injury. Figures 1 and 2 show typical profile recordings taken before and after phentolamine

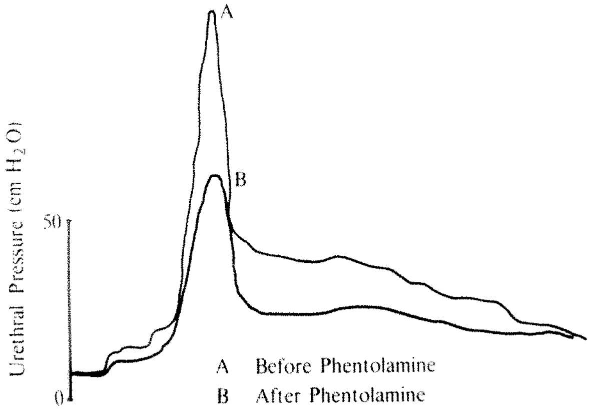

Fig. 1 The effect of phentolamine on the urethral pressure profile recorded in a patient with a C6 tetraplegia.

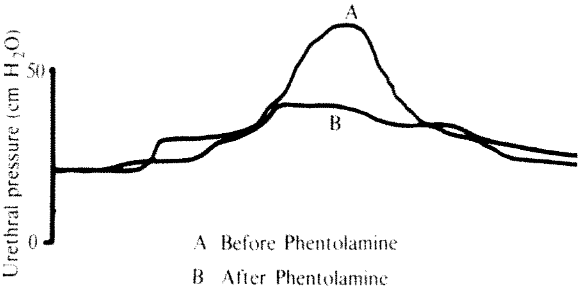

Fig. 2 The effect of phentolamine on the urethral pressure profile recorded in a patient with a conus medullaris lesion.

in cervical and in conus lesions. A considerable drop in the peak pressure is evident in each case.

The mean effect of phentolamine in each of the 4 groups is listed in Table 2.

From these results a histogram showing the relative proportion of smooth muscle contribution to the urethral pressure at different levels of spinal injury has been constructed (Fig. 3).

If these values are compared to the phentolamine response found in normal individuals, then a significantly increased smooth muscle contribution to the urethral profile is found in group 2 ($p < 0.02$) and group 3b ($p < 0.05$). In group 1 the value approaches statistical significance ($t = 1.83$) whilst in group 3a no significant difference is found ($t = 0.6$).

Table 3 The Postural Change in the Urethral Pressure Profile at Different Levels of Spinal Injury, in 21 Patients from the Main Series

Group	*No. pts.*	*Mean MUP*		*Mean IV pressure*	
		Supine	*Sitting*	*Supine*	*Sitting*
1	6	73.3	87.1	5.5	16.8
2	6	106.1	121.6	7.0	19.6
3a	3	65.3	130.3	18.6	34.3
3b	4	59.5	77.0	4.5	16.2
4	2	52.5	98.5	10.0	24.5

Table 4 The Postural Change in "Failed DES" Cases

Case No.	*Spinal level*	*MUP*		*Intra-vesical pressure*	
		Supine	*Sitting*	*Supine*	*Sitting*
1	C6	31.0	71.0	7.0	18.0
2	C5	104.0	163.0	26.0	32.0
3	C6	29.0	115.0	6.0	23.0
4	T8	54.0	94.0	7.0	33.0
5	C7	104.0	165.0	12.0	29.0
6	C6	85.0	98.0	8.0	19.0

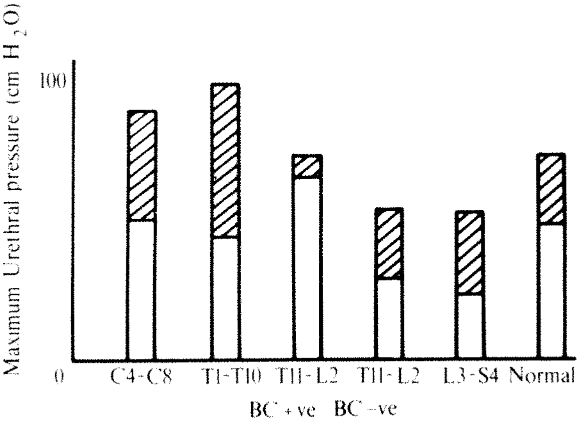

Fig. 3 Histogram showing the relative proportion of smooth muscle at different levels of spinal lesion. (The shaded area represents the smooth muscle component of urethral pressure.)

The Effect of Posture

(*a*) Postural change in the maximum urethral pressure at different levels of spinal injury

The increase in the maximum urethral pressure in response to a change in posture is shown in Table 3, from which a histogram (Fig. 4) has been constructed.

The change in maximum urethral pressure in relation to the change in intravesical pressure is shown in the scatter diagram (Fig. 5).

(*b*) Postural change in "Failed DES" cases

Table 4 shows the postural change in these 6 cases together with the level of the neurological lesion.

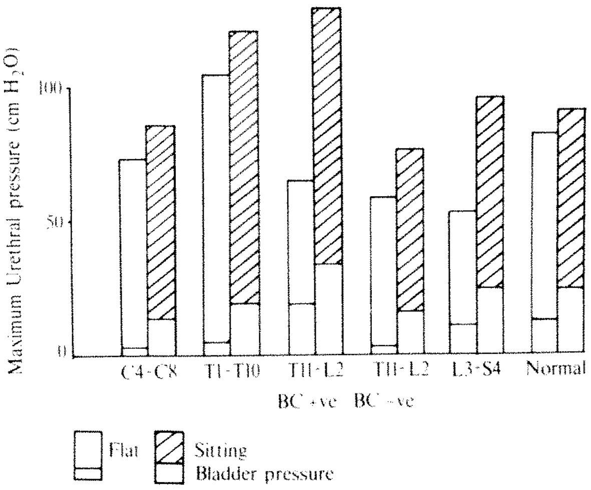

Fig. 4 Histogram showing the mean change of the maximum urethral pressure in response to a change in posture.

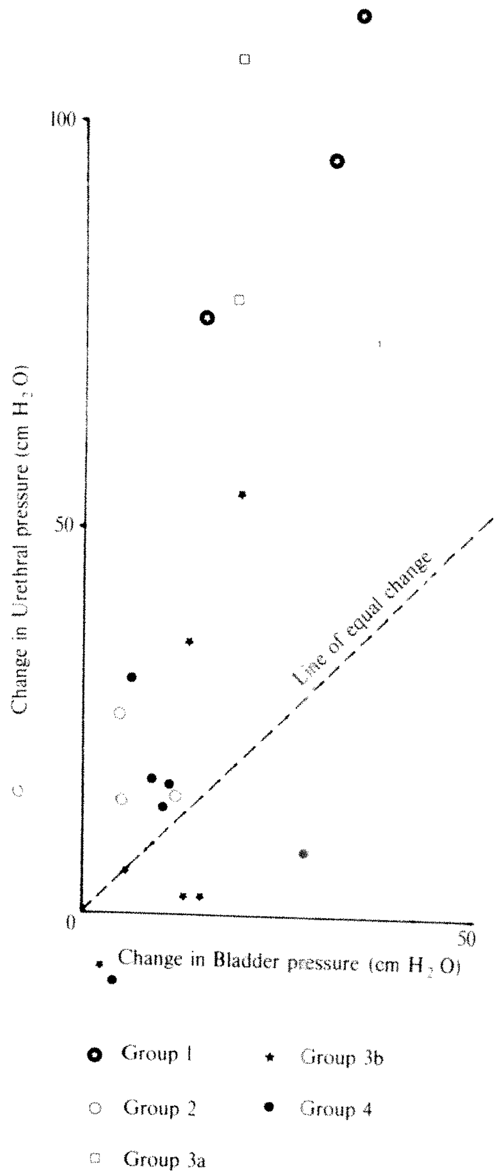

Fig. 5 Scatter diagram showing the postural increase in urethral pressure against the increase in intravesical pressure.

There was neither a consistent change in pelvic floor electromyograms, nor any correlation between urethral pressure changes and altered EMG discharges resulting from a change of posture.

The Effect of Phentolamine on the Postural Response

(*a*) The main series

The reduction in the maximum urethral pressure when in the sitting position following alpha blockade in 8 cases from the main series is shown in Figure 6, with a comparison of the postural increase in pressure with the subsequent phentolamine effect.

(*b*) "Failed DES" cases

Figure 7 shows typical urethral pressure profiles demonstrating the return of a pressure peak on assuming the sitting position, in a patient in whom division of the external sphincter had been unsuccessful. The response to phentolamine, resulting in a flat profile without a pressure peak, is also shown. The postural effect in each of the 6 cases of "Failed DES" is shown in Figure 8, together with the subsequent drop in pressure following the intravenous administration of phentolamine. Case No. 6 demonstrates the effect

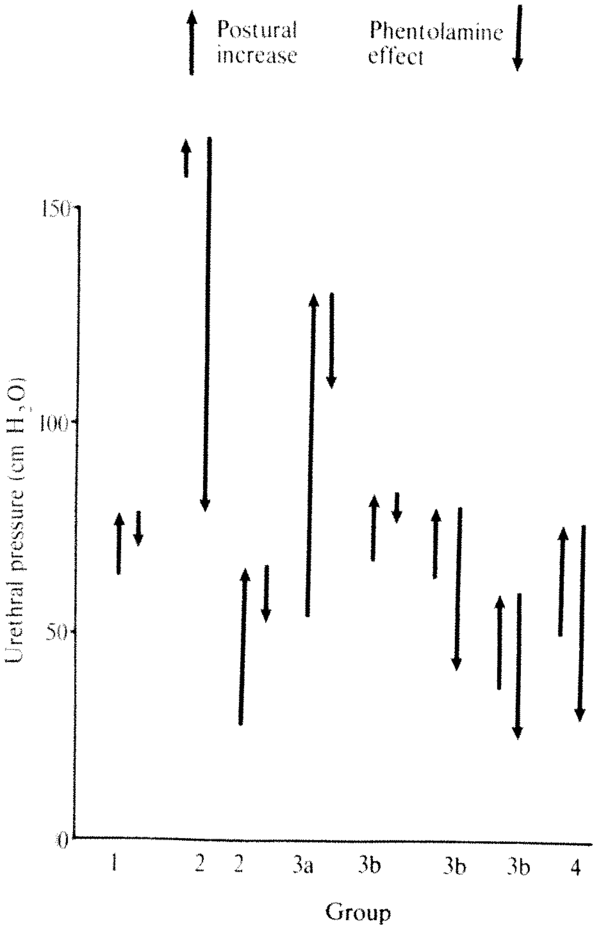

Fig. 6 The posture change in the maximum urethral pressure in 8 cases from the main series, together with the subsequent phentolamine effect.

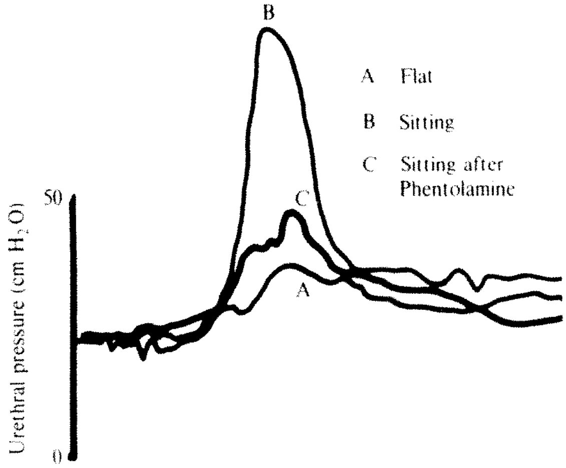

Fig. 7 The postural change in the urethral pressure profile in a "Failed DES" case with the subsequent phentolamine effect.

of bladder mucosal anaesthesia upon the postural increase in pressure, and also the further reduction in pressure as a result of alpha-adrenergic blockade.

Blood Pressure Responses

A mean drop of 15 mm Hg of both systolic and diastolic blood pressure was recorded, the decrease being noted prior to the urethral responses.

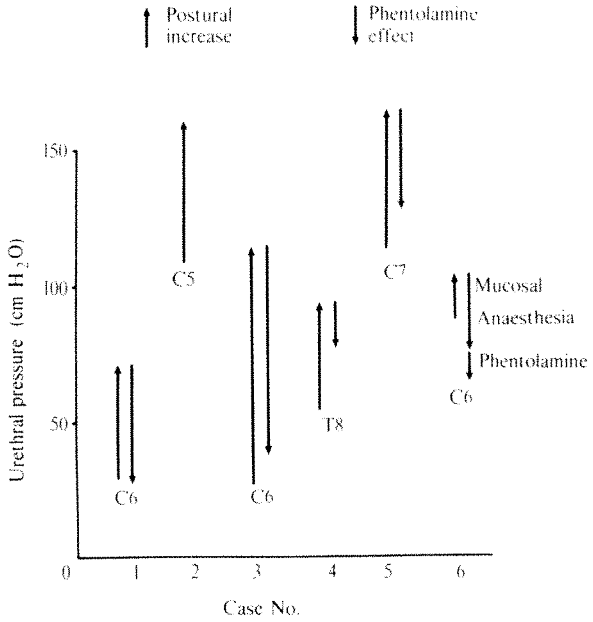

Fig. 8 The postural increase and phentolamine effect in 6 "Failed DES" cases. Case No. 6 shows the effect of bladder mucosal anaesthesia.

Discussion

In order that voiding can take place in patients with spinal cord injuries 2 conditions must apply. First, the bladder neck must be opened either by detrusor contraction, albeit reflex or uninhibited as is the case in supra-sacral lesions, or by abdominal straining augmented by bladder neck resection as in the case of sacral lesions. Second, the resistance in the membranous urethra must remain below the intravesical pressure. When assessing the urethral response in neuropathic vesico-urethral dysfunction, it is perhaps more relevant to refer to the maximum urethral pressure, rather than to the more commonly reported urethral closure pressure as defined by the International Continence Society (1976).

Recent studies have shown the importance of the urethral plain muscle contribution to the normal urethral pressure profile both in animals and in man (Donker *et al.*, 1972; Awad and Downie, 1976), and that this muscle is under alpha-adrenergic sympathetic control. Furthermore, reported cases with cauda equina lesions have shown that urethral plain muscle activity can cause outflow obstruction (Abel *et al.*, 1974) and that this may be relieved by alpha-adrenergic blockade. Other authors have reported the beneficial use of alpha-adrenergic blocking agents in neuropathic bladder dysfunction when voiding has been impaired despite adequate detrusor contractions (Krane and Olsson, 1973; Mobley, 1976). The precise action of the pharmacological agent has not previously been determined, nor has the response in relation to the level of spinal injury been reported.

The results of this study have shown that a considerable proportion of the maximum urethral pressure is derived from smooth muscle activity under alpha-adrenergic control, at all levels of spinal lesion. The contribution by smooth muscle is greater than that found in normal individuals, provided that the lesion does not directly involve the sympathetic outflow to the bladder and urethra. Patients in whom the bladder and urethral spinal sympathetic efferents are involved show differences in the configuration of the profile, and this appears to be dependent upon the integrity of the sacral parasympathetic reflex arcs.

The sympathetic nerve supply to the bladder and urethra arises from the lower thoracic and upper lumbar spinal segments although there may be further efferents from higher segments travelling through the paravertebral ganglia. Studies of Elbadawi and Schenk (1974) have suggested that the intra-mural sympathetic neurons of the bladder and urethra are influenced by both adrenergic (presumed sympathetic) and cholinergic (presumed parasympathetic) efferents, and that there is a modulating influence of 1 system upon the other in the control of vesico-urethral function (Elbadawi and Schenk, 1971). The pattern of dual sympathetic-parasympathetic innervation of the bladder base and urethra has been confirmed by Dixon and Gosling (1974). As the sympathetic supply to the bladder and urethra leaves the spinal cord above the cholinergic efferents in the conus medullaris, spinal injuries at different levels can produce lesions involving either one or other of the autonomic divisions, or both together.

In high spinal lesions, when both sympathetic and parasympathetic systems are decentralised, approximately half of the maximum urethral pressure is derived from smooth muscle. If the level of lesion involves the specific segments of the bladder sympathetic supply but spares the sacral reflex arcs, there is a very much reduced alpha-adrenergic response. This perhaps indicates persistent cholinergic inhibitory modulation upon urethral smooth muscle. When the sacral arcs are involved together with the sympathetic outflow, then relatively more alpha-adrenergically innervated smooth muscle activity is noted. Similarly, if the adrenergic outflow is undamaged but the cholinergic efferents involved, then an increased alpha-adrenolytic response is once more recorded. In both these situations the smooth muscle has been released from cholinergic inhibition. These results would therefore further support the modulation hypothesis.

It is clear that smooth muscle in the urethra is an important element in outflow obstruction at all levels of spinal injury, and conversely that striated muscle seems relatively less important. This is confirmed to some extent by the failure to correlate the pelvic floor electromyogram recordings with a change in profile height. Furthermore, the profiles after alpha blockade in supra-sacral lesions do not differ significantly from normal values after alpha blockade, suggesting that the striated component to the total profile is not in excess. In sacral lesions, however, with flaccidity of the pelvic floor, the profile heights are significantly lower than normal, the difference being a reflection of the somatic component to urethral pressure.

That there is an increase in urethral pressure with a change of posture from the supine to the sitting position in normal individuals has been observed by several workers. (Lapides *et al.*, 1960; Tanagho *et al.*, 1966; Griffiths, 1973; Edwards and Malvern, 1974; Andersen and Bradley, 1976.) The explanation for this increase has been based on 2 hypotheses. Contraction of the pelvic floor muscles has been implicated by Lapides *et al.* (1960), and Tanagho *et al.* (1966), as the postural rise in the intra-urethral pressure recorded by them was similar to the increase produced by voluntary contraction of the peri-urethral striated muscles, and was greater than either the increase in intra-vesical or intra-abdominal pressure. The alternative explanation derives from the fact that as the membranous urethra is largely intra-abdominal, increases in abdominal pressure are transmitted equally to bladder and urethra (Enhorning, 1961); thus the intra-vesical and the intra-urethral pressure increases resulting from a change of posture are identical (Edwards and Malvern, 1974; Andersen and Bradley, 1976). Griffiths (1973), however has shown that the intra-urethral pressure rise is only 75% of that recorded in the bladder on assuming an erect position, due to the disproportionate transmission of abdomina pressure.

In neuropathic bladder dysfunction, an increase in urethral pressure due to a change of posture has also been reported. Vincent (1966) suggested that the increase seen in patients with sacra lesions was due to "bunching" and angulation o the membranous urethra against the perinea membrane as the bladder and prostate prolapsed downwards between the flaccid levatores ani This concept was confirmed radiologically in case by Dollfus *et al.* (1972). Observations o increased urethral pressure resulting from a change of posture were not confined to sacra cases with flaccidity of the pelvic floor, bu included supra-sacral lesions as Gibbon (1973 showed an increase in retrograde urethral resist ance in the upright position "whatever the degre of sacral activity".

The observations in this series have shown tha there is a postural increase in maximum urethra pressure, in excess of the change in intra-vesica pressure, at all levels of spinal lesion. Further more, there is a particularly marked postural res ponse in patients whose spinal injury involved the region of sympathetic outflow to the bladder and urethra but spared the sacral parasympathetic arcs (group 3a). "Failed DES" cases also show that there is a return of a pressure peak on sitting and that this may be abolished by alpha-adrenergic blocking agents.

There are 2 possible explanations for this postural phenomenon. Striated muscle may be responsible, when contraction of the pelvic floor is induced by the stimulus of abdominal pressure acting upon it. If this were the case then it would be expected that the upper spinal lesions (groups 1 and 2) would show the same response as the lower thoracic and upper lumbar lesions (group 3a) in whom the pelvic floor reflex arcs remain intact, and no postural response would be evident in sacral lesions with flaccid peri-urethral striated muscle. The possibility of a second mechanism thus arises, and involves the active contraction of urethral smooth muscle in response to a change of posture. The observed results in the "Failed DES" cases would suggest that smooth muscle is involved, as the peak of pressure, evident only in the upright position, was abolished by phentolamine. Similarly, in those cases where the phentolamine response was measured in the sitting position, the postural increase in urethral pressure virtually matched the subsequent phentolamine effect.

The postural increase in smooth muscle tone may be explained in 2 ways. A release from inhibition of an autonomic reflex arc may be responsible. Many reflexes associated with micturition have been described (Barrington, 1931, 1941; Bors and Comarr, 1971) but all involve intact pelvic and/or pudendal nerves. Shisito *et al.* (1963) have postulated the presence of a sympathetic reflex concerned with micturition, with a sacral afferent and hypogastric efferent, but in conus and cauda equina lesions this reflex would be interrupted. There may be receptors in the bladder or pelvic floor completing a reflex arc with hypogastric afferents and efferents (Bors, 1977) and therefore bladder anaesthesia was employed to determine whether this had any effect on urethral smooth muscle tone. Of the 2 patients studied, 1 (with a cervical cord lesion) showed an appreciable drop in the maximum urethral pressure following anaesthesia, whilst the other (with a conus lesion) showed a smaller drop. The subsequent response to phentolamine, greater in the second patient, indicated that there was still smooth muscle activity in the urethra after bladder mucosal anaesthesia.

An alternative explanation for a postural increase in urethral smooth muscle activity may lie in the altered response of muscle following denervation. A "decentralisation supersensitivity" to circulating catecholamines may be the mechanism involved. There is evidence that circulating catecholamines increase on assuming an upright position in both normal (Vendsalu, 1960), and spinal cord injury patients (Guttmann *et al.*, 1963). Although the response in spinal injury patients is less than that observed normally, the lower the lesion of the spinal cord, the greater is the increase in catecholamines resulting from a change of posture. The sympathetically decentralised muscle could be exhibiting an increased sensitivity of the adrenergic receptors to noradrenaline thus causing an increase in smooth muscle tone. This phenomenon would account for the maximal postural effect observed in group 3a, in which sympathetic decentralisation of the bladder is more specific, and in which the postural increase in circulating catecholamines is greater, in comparison with higher spinal lesions. It would also follow that the postural effect in patients with lesions below L2 would be small, as the sympathetic supply is undamaged, were it not for removal of cholinergic inhibition which allows smooth muscle contraction.

There are pitfalls in a urostatic investigation of urethral function, primarily as the method of investigation does not necessarily reflect what happens during voiding, when further local vesico-urethral reflexes play a part in smooth muscle function (Ghonheim *et al.*, 1975a, b). Further, beta-adrenergic responses, which have been shown to be inhibitory to the urethra, are difficult to study in isolation and have been ignored in this study, although they may have a role in disordered urethral function.

Conclusions

There is a significant smooth muscle contribution to the urethral pressure profile in patients with neuropathic vesico-urethral dysfunction.

The extent of this contribution bears a relationship to the level of the spinal lesion in respect of the sympathetic efferents from the spinal cord.

Smooth muscle plays an important part in outflow obstruction, particularly so in relation to increased urethral tone secondary to a change of posture, and this increase may be humorally mediated.

A sound rationale for the use of alpha-adrenergic blocking agents in neuropathic bladder dysfunction is presented.

Addendum

Preliminary results have shown that a postural urethral response can be reproduced by a simulated change of posture in the supine position, produced by partially occluding venous return in both legs using sphygmomanometer cuffs. The increase in urethral pressure produced in this way is similar to the true postural change, and appears to be closely related to changes in circulating catecholamine levels as measured by a trihydroxyindole fluorescent technique (Turton and Deegan, 1973).

Some female patients with low urinary flow rates, but normal detrusor voiding pressures, have demonstrated this postural urethral response. The increase in urethral pressure can be reproduced with venous occlusion cuffs and, whilst these patients have no clinically detectable neurological disease, the basic pathology may be a hitherto unrecognised isolated urethral neuropathy, with abnormal smooth muscle contraction occurring due to increases in catecholamine levels as a consequence of cardiovascular homeostasis.

The results of these further investigations would tend to support the hypothesis that urethral smooth muscle is exhibiting a "supersensitivity", and will be reported in full in a future communication.

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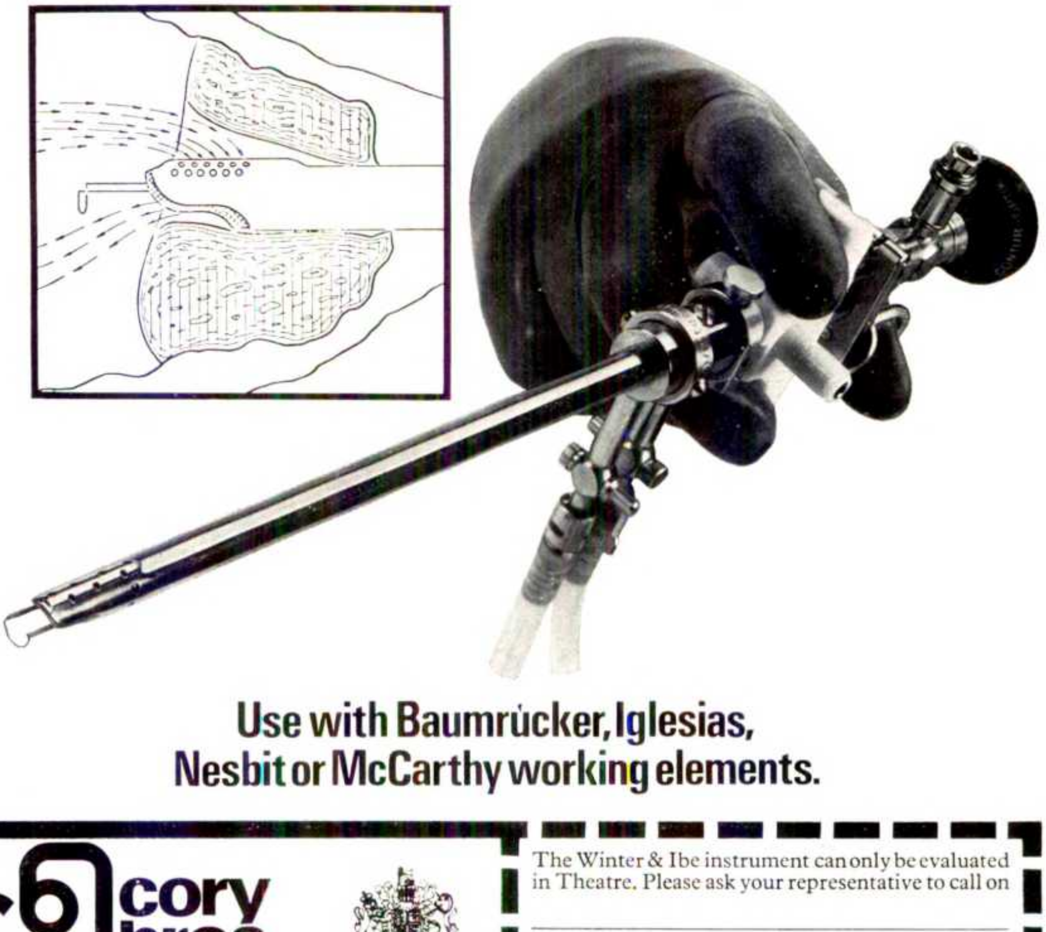

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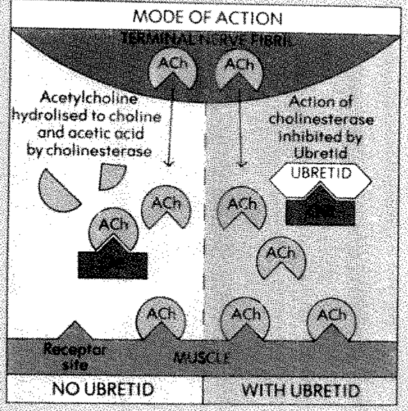
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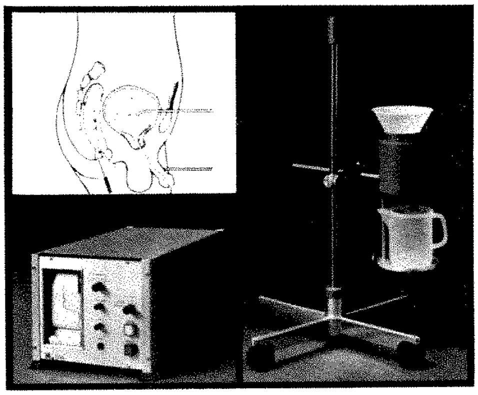

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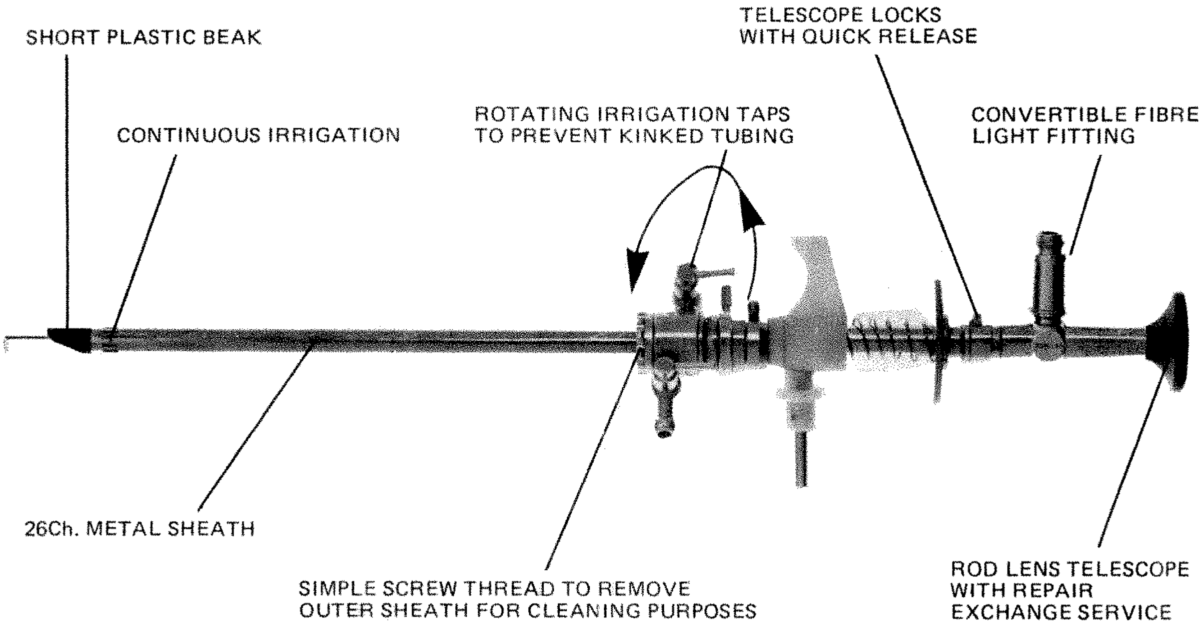
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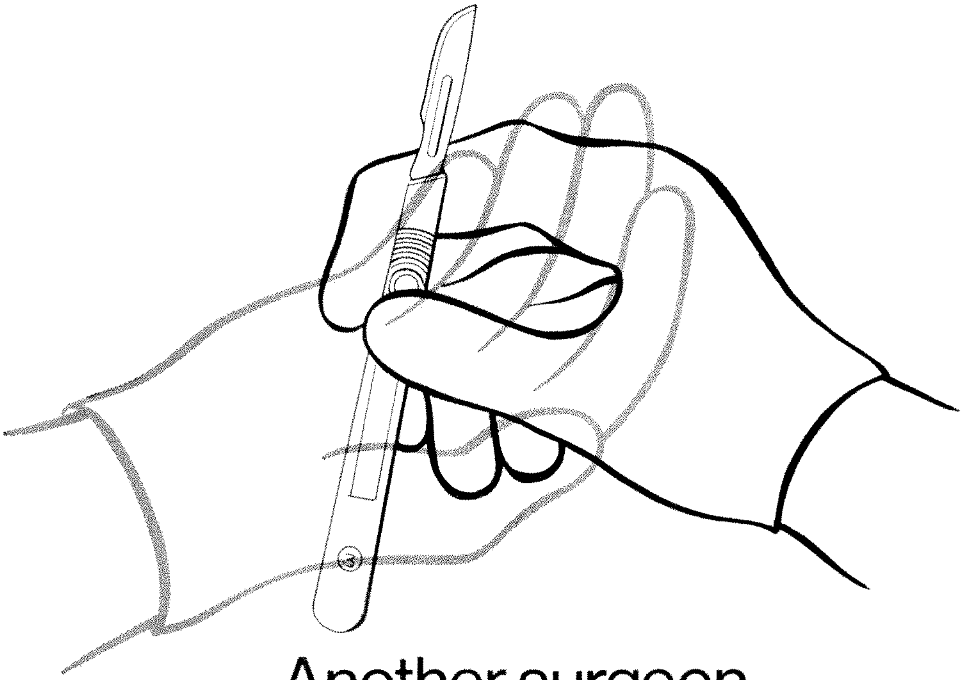

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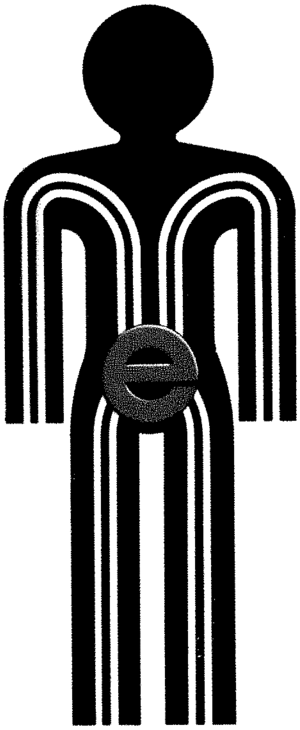

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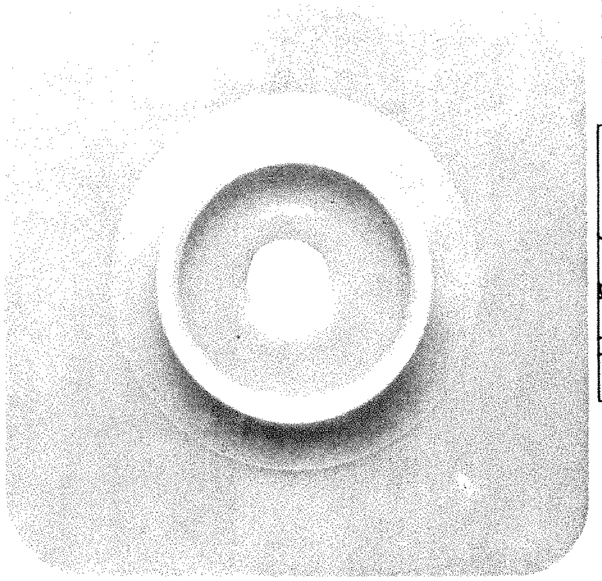

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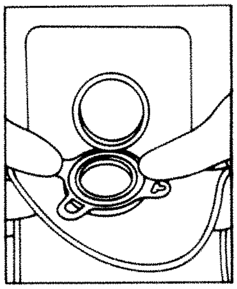

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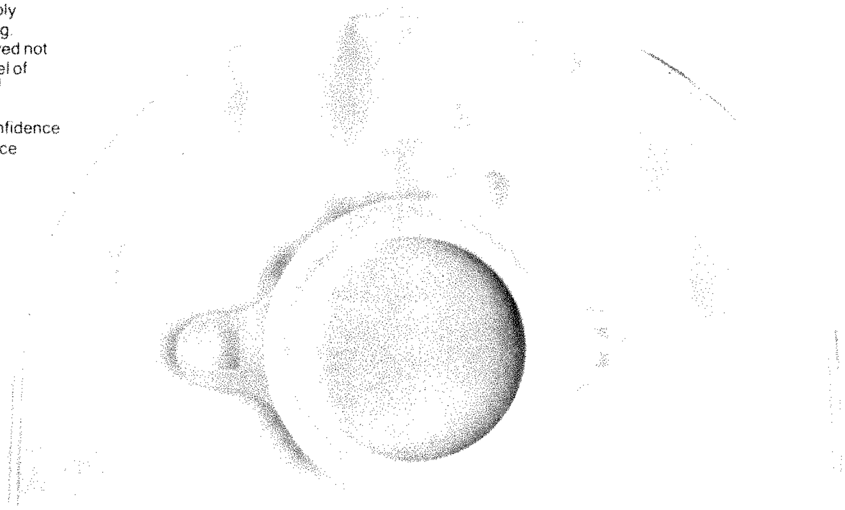

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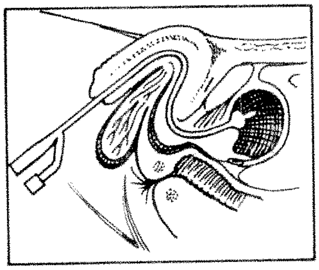

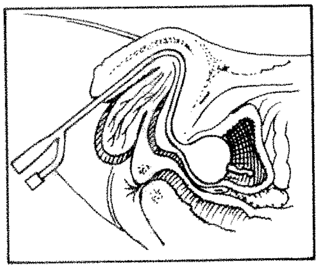

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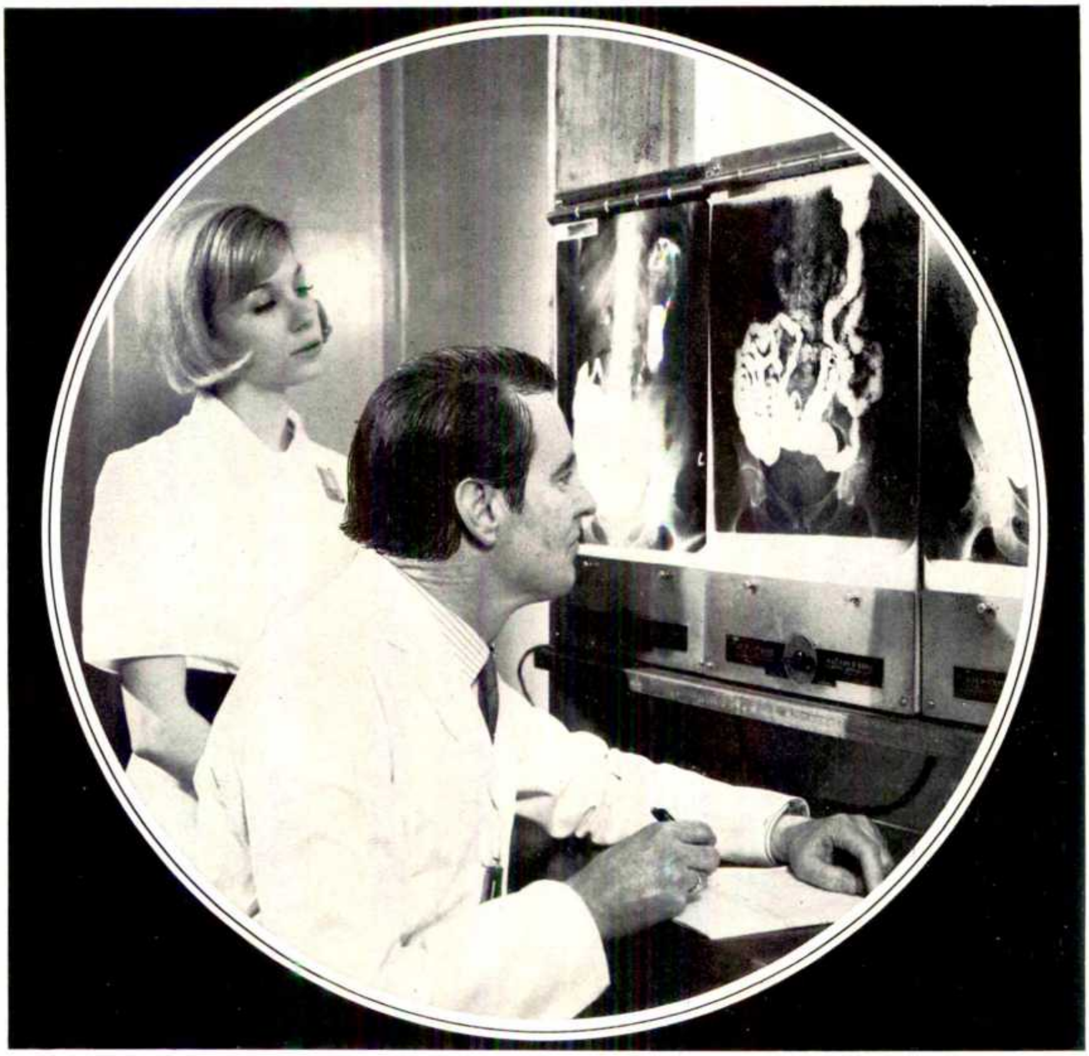

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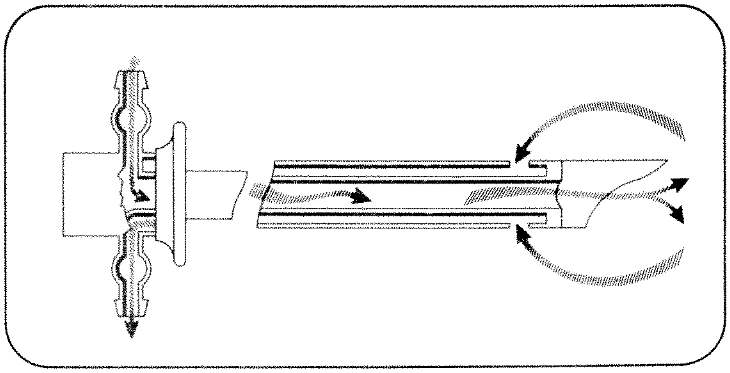

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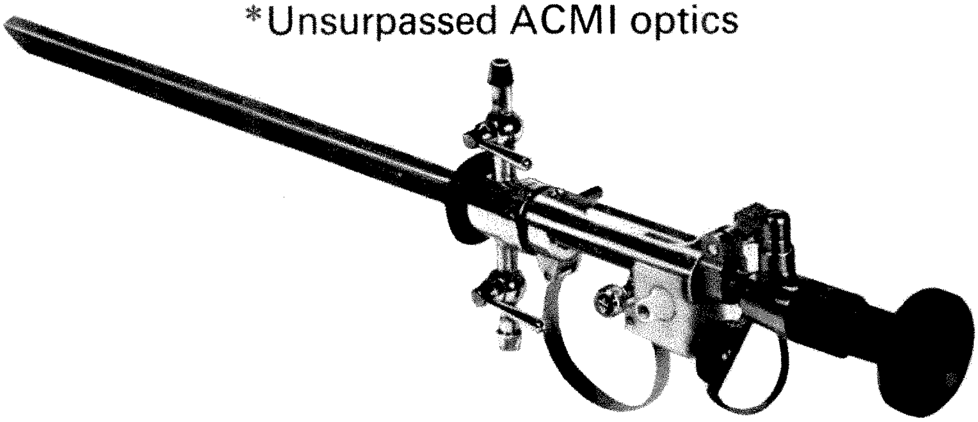

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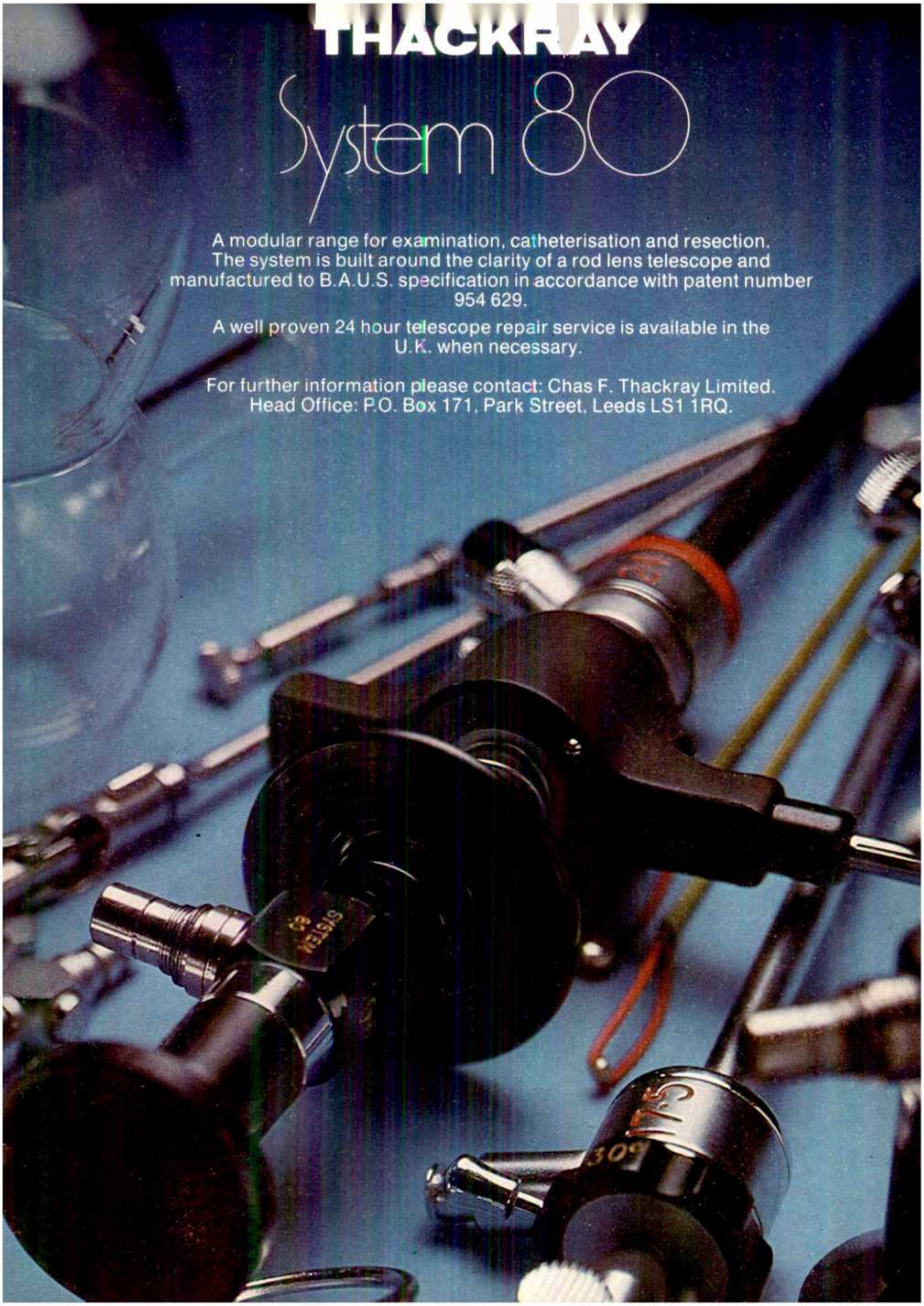

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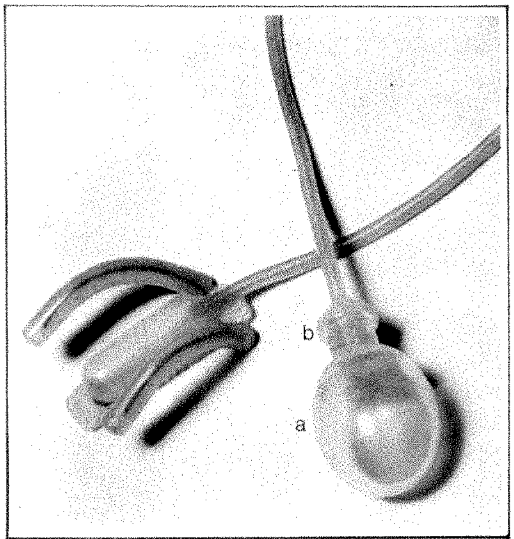

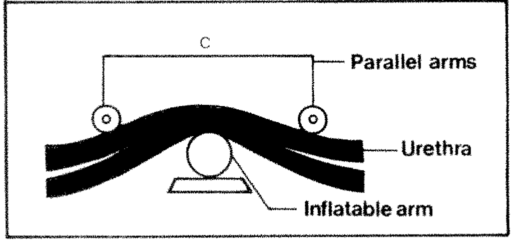

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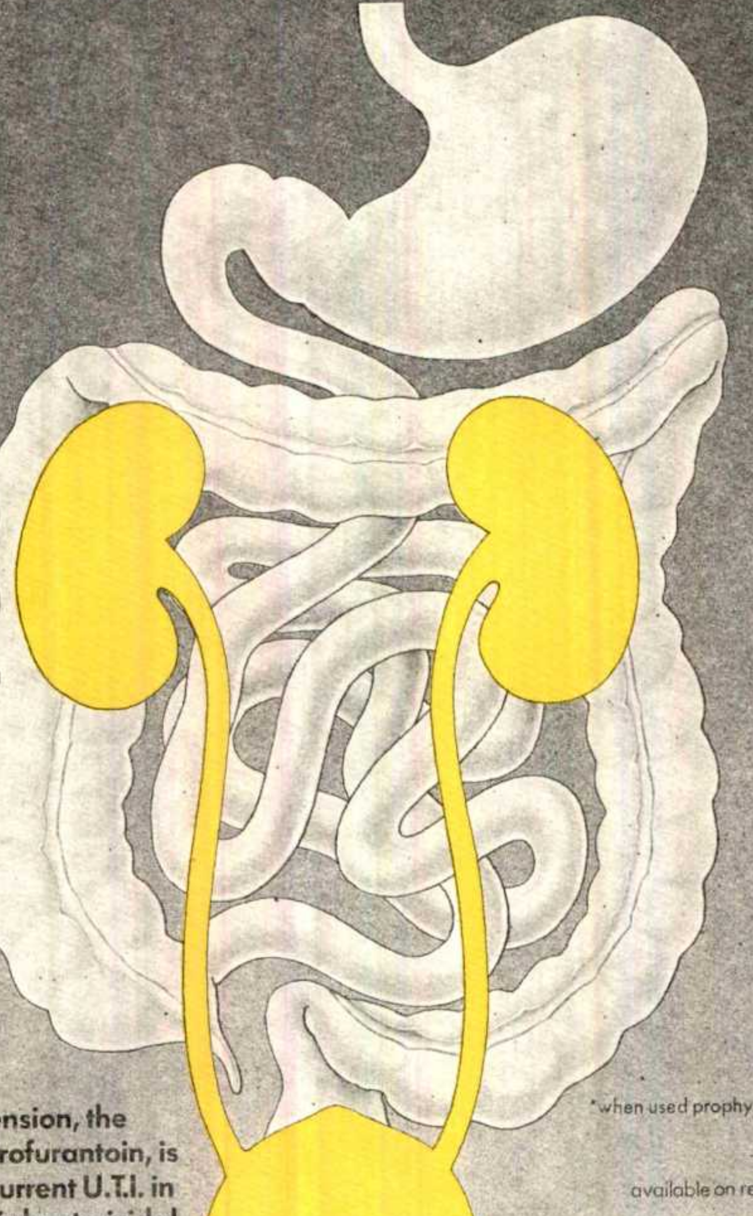

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British Journal of Urology

May 1978 Volume 50 Number 3

Original Articles

145 Functional Obstruction of the Ureter and Renal Pelvis. A Histological and Electron Microscopic Study
J. A. Gosling and J. S. Dixon

153 Pre-operative Balloon Occlusion of the Renal Artery for Radical Nephrectomy
A. D. Mee and S. W. Heap

157 An Unusual Case of Persistent Renal Collar in a Human Adult Male
Beverley Kramer

160 The Influence of Wound Drainage on the Infection Rate in Kidney Transplant Patients
Steen Walter, Lars Rytter Poulsen, Michael Friedberg and René Vejlsgaard

162 Delayed Rupture of the Bladder
A. R. Turnbull, C. J. Smart and J. D. Jenkins

164 A Radioisotope Method of Assessing Uretero-ureteric Reflux
P. H. O'Reilly, R. S. Lawson, R. A. Shields, H. J. Testa, E. Charlton Edwards and R. N. P. Carroll

169 Has Bromocriptine a Place in the Treatment of the Unstable Bladder?
K. P. J. Delaere, F. M. J. Debruyne and W. A. Moonen

172 Bone Scanning and Plasma Phosphatases in Carcinoma of the Prostate
E. P. N. O'Donoghue, A. R. Constable, T. Sherwood, J. J. Stevenson and G. D. Chisholm

178 The Role of Bone Scanning in the Assessment of Prostatic Carcinoma
B. McGregor, A. G. S. Tulloch, M. F. Quinlan and F. Lovegrove

182 The Effect of Routine Digital Examination of the Prostate on Serum Acid Phosphatase
A. N. Khan, G. S. Lee, D. M. R. Jackett, R. G. Newcombe and M. S. Pathy

185 The Significance of Bone Marrow Acid Phosphatase in Patients with Prostatic Carcinoma
Sophie Dorothea Fossa, Jerzy Sokolowski and Liv Theodorsen

190 Outflow Obstruction in Neuropathic Bladder Dysfunction: The Neuropathic Urethra
G. Sham Sunder, K. F. Parsons and N. O. K. Gibbon

200 Reflex Urethral Instability
Edward J. McGuire

205 Visualisation of the Lymphatics of the Vulva and Scrotum by Direct Intratissue Injection of the Dye
L. Vlahos, G. Karatzas, A. Giannopoulos, V. Benakis, C. Dimopoulos and G. Pontifex

Case Reports

209 Foreign Body Migrating to the Kidney
Gary M. Stack, Michael E. Mayo and Mark D. Kiviat

[*Continued on Inside Back Cover*]

210 Busulphan Haemorrhagic Cystitis
R. J. Millard

211 Epididymal Sarcoidosis
J. C. Heffernan and W. K. Blenkinsopp

212 Bilateral Renal Carcinoma with Metastasis in Gall Bladder and Associated with a Strongly Positive ANA
J. Osman, R. J. Regan and J. R. E. Dathan

213 A Cyst in the Penis of a Child
C. Laurenti and C. De Dominicis

214 Calyceal Injury due to External Ureteric Compression during Urography
R. A. Appell, D. H. Bagley, D. E. Shield and E. J. McGuire

215 Ectopia Testis Transversa
Abdul Ahad, Nazir A. Wani, Bansi L. Bhan, and Ravinder K. Garyali

216 Conferences and Courses

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Case Report

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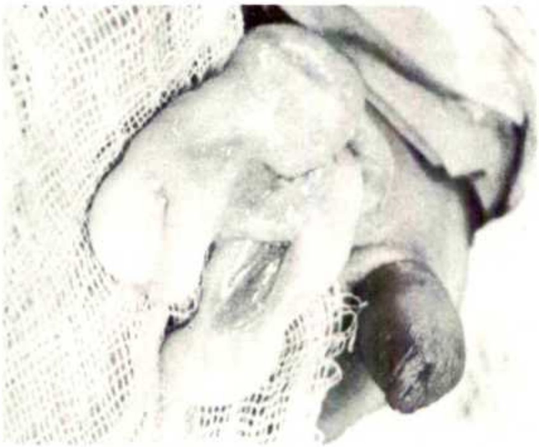

Fig.

Comment

Ectopia testis transversa is a rare congenital testicular anomaly. Gupta and Das (1960) have suggested various possible mechanisms for this anomaly and Mukerjee and Amesur (1965) while reviewing 25 cases in the world literature have proposed another. Sastry *et al.* (1974) have added a further case to the series, and we are reporting 1 more.

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Mukerjee, S. and Amesur, N. R. (1965). Transverse testicular ectopia with unilateral blood supply. *Indian Journal of Surgery*, **27**, 547.

Sastry, S. C., Venkatiswarlu, K. and Altaf Hussain, B. (1974). Transverse testicular ectopia. *International Surgery*, **59**, 373-374.

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British Journal of Urology (1978), **50**, 214

Calyceal Injury due to External Ureteric Compression during Urography

Incomplete filling of the collecting system presents a serious problem in evaluation and interpretation of urograms. External ureteric compression (EUC) during excretory urography has been offered as a technique to produce partial urinary stasis and to delay the outflow of contrast material in order better to visualise the collecting system without complication (Daughtridge, 1965). A case of pyelosinus extravasation of contrast material during excretory urography is presented as a complication of EUC that must be considered when interpreting urograms.

Case Report

A 24-year-old Caucasian male was evaluated at Yale-New Haven Hospital for complaints of cloudy urine, hesitancy in initiating voiding, low back and perineal pain, and a history of having had similar symptoms 2 years previously, at which time he was treated for prostatitis. Physical examination revealed prostatic tenderness per rectum. Although urinalysis showed 10-18 white blood cells per high-powered field microscopically, culture of the urine failed to demonstrate bacterial growth. Empirical treatment of the patient for the diagnosis of prostatitis resulted in the resolution of his symptoms. Excretory urography at 3 min demonstrated bilateral function. At this point EUC by the Daughtridge technique was instituted and pyelosinus extravasation of contrast material from the lower of 2 middle calyceal systems of the right kidney was noted. The patient suffered transient right-flank pain and no other observable sequelae. Repeat excretory urography 1 week later without EUC revealed a normal excretion pattern with superimposition of anterior and posterior infundibula in this same lower-middle collecting system on the right.

Comment

Clearly, this patient did not need EUC during excretory urography to evaluate his upper urinary tracts. However, the case does serve to demonstrate that EUC may cause the very hazards it is meant to prevent—the possibility of erroneous diagnosis and further procedures. The mass effect from contrast seen in the EUC film could be misinterpreted as a lesion with pyelocancerous backflow (Copeland *et al.*, 1976). Fortunately the repeat excretory urogram confirmed the absence of any lesion and the patient was not subjected to further investigations.

Pyelotubular backflow is a normal finding in EUC, whereas pyelosinus extravasation is never a normal finding and is the result of actual rupture of the calyceal fornix. It should be recognised that EUC may cause such extravasation in the complete absence of any demonstrable lesion.

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British Journal of Urology (1978), **50**, 213

A Cyst in the Penis of a Child

Cysts in the penis are a rare occurrence. They are either congenital or acquired. The former are situated in the midline on the underside of the penis or near the frenulum, and known as cysts of the raphe. Histologically they are covered with a cuboidal or cylindrical epithelium and contain a serous mucous substance, or they are epidermoid cysts, as in our case, or dermoid with an atheromatous content. The acquired cysts are of traumatic or surgical origin and as such do not have an elective location.

Case Report

A 14-month-old male came to our attention because the parents noticed that since birth the child had a cherry-size growth in the central area of the penis. Examination (Fig.) revealed a mass, approximately 3 cm in diameter, the covering skin of which had a normal appearance. The mass was located on the right latero-dorsal zone of the penis in the proximal half, and the penis itself appeared to be slightly deviated towards the opposite side, particularly during erection. The mass was found to be fairly mobile at the upper levels and much less mobile at the lower levels. It was painless, had a smooth surface and an elastic consistency. It did not extend on to the ventral side of the penis and did not come into contact with the median raphe. Trans-illumination was positive. A narrow catheter introduced into the urethra confirmed that the latter was not involved. Haematochemical and urographic findings were normal. Having established the cystic nature of the mass it was decided to proceed with surgical removal. After sectioning a vascular pedicle at the base of the penis, the cyst was removed intact.

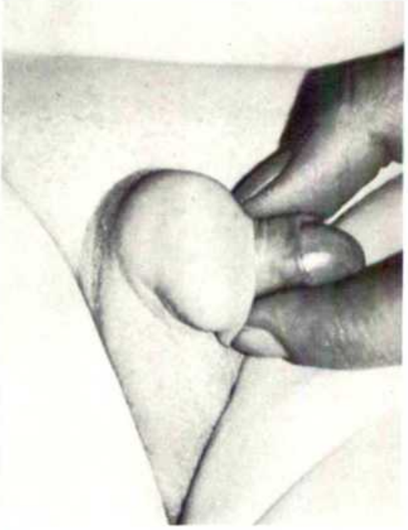

Fig.

Upon opening the sac, 3 ml of a milky liquid was found which at microscopic examination presented numerous squamous cells and horn lamellae. Culture of the liquid was negative. Histological examination revealed that the wall of the cyst was lined with a squamous epithelium and the diagnosis of epidermoid type cyst of the penis was made.

Comment

The cyst observed does not appear to fit into the usual classification since congenital cysts are usually situated on the midline raphe. This cyst had no connection with the raphe, and its vascular pedicle originated at the base of the penis on the dorsal side.

Therefore, this cyst can be classified as a congenital dorsal cyst of the penis of epidermoid type.

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British Journal of Urology (1978), **50**, 212

Bilateral Renal Carcinoma with Metastasis in Gall Bladder and Associated with a Strongly Positive ANA

Case Report

A 56-year-old woman was referred in October 1974 with deteriorating renal function, a high ESR, weight loss, left loin pain and mild persistent fever. In 1971 hypertension and proteinuria were noted. In 1973, IVP showed normal kidneys and calcification in the region of the gall bladder. Because of right hypochondrial pain cholecystectomy was done. The gall bladder contained pigment stones and a polypoid tumour which histologically was considered a benign hamartoma.

On admission, serum creatinine was 330 mol/l, haemoglobin 10.1 g/dl and ESR 123 mm. The urine contained protein and scanty red cells. Serum antinuclear antibody (ANA) was present in a titre of 1 : 1280. LE cells were negative. DNA binding antibody was 19% (normal). IVP showed no change from 1973. Glomerulonephritis was considered likely but a renal biopsy showed only chronic interstitial nephritis. Review of the gall bladder histology showed a clear cell carcinoma of probable renal origin. Bilateral renal arteriograms demonstrated extensive tumour circulation in both kidneys (Fig.). The patient died 3 months later.

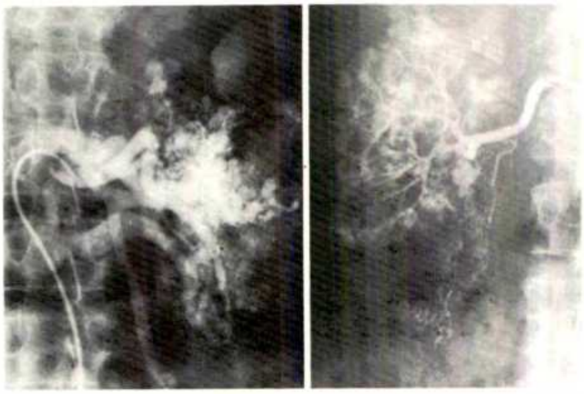

Fig. Right and left renal arteriograms showing tumour circulation in both kidneys.

Comment

Gall bladder metastases are uncommon in cases of renal carcinoma. The incidence was 0.06% in 1 large series (Bennington and Kradjan, 1967). Renal carcinomas are not infrequently bilateral. Wright (1975) found 80 cases in the literature. He recommended bilateral angiography in patients with suspected renal carcinoma because of the therapeutic implications. With regard to the patient's positive ANA, none of the drugs she had received is associated with a lupus syndrome. ANA can occur in association with malignant disease. In 8 cases of renal carcinoma in 1 study of malignancies, ANA was present in 4 (Whitehouse and Holborow, 1971). We feel, therefore, that malignancy should be considered in any patient with an unexplained positive ANA.

Acknowledgements

Thanks are due to Dr P. Guyer for his radiological advice and to Dr A. McIver who reviewed the histology.

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British Journal of Urology (1978), **50**, 211

Epididymal Sarcoidosis

Case Report

A Negro male, aged 35 years, presented with uveoparotid fever, and a cervical lymph node showed the typical granulomas of sarcoidosis. Mantoux tests were negative. Steroid therapy relieved his uveoparotid fever, and has been continued to the present. Two years later the right epididymis was biopsied for painful enlargement; this also showed typical periductal non-caseating granulomas (Fig.), and culture for mycobacteria and fungi was negative. He has also had nasal obstruction and dermal nodules, both tissues showing sarcoidosis on biopsy, but no hilar lymphadenopathy.

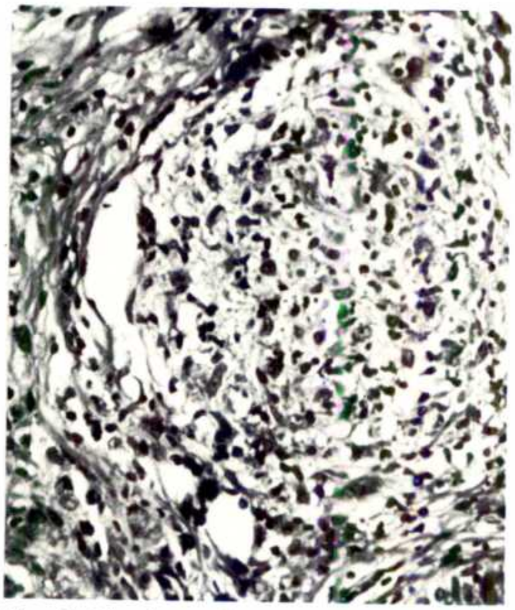

Fig. Periductal granulomas in epididymis. Haematoxylin and eosin (×270).

Comment

The commoner causes of non-caseating granulomas of the epididymis are sperm granuloma, identified by the presence of spermatozoa, and granulomatous epididymitis, in which the granulomas are intraductal. Epididymal sarcoidosis is rare: Rudin *et al.* (1974) found only 11 reported cases confirmed by biopsy, and as in the present case steroids have had little or no effect. No clinical epididymal lesions were found in 195 cases of sarcoidosis, although epididymal granulomas have been found in 1 of 22 cases (Ricker and Clarke, 1949) and in 2 of 30 cases (Longcope and Freiman, 1952) at necropsy.

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British Journal of Urology (1978), **50**, 210

Busulphan Haemorrhagic Cystitis

Case Report

A 59-year-old man presented with initial haematuria of several days duration and no other symptoms. He had had intermittent courses of busulphan to a total dose of 1.98 kg, for the control of chronic myeloid leukaemia since 1973. The urine was sterile but contained 100 RBC/ml. Platelet count was normal. An IVP showed no abnormality. At cystoscopy he was found to have multiple dilated vessels and submucosal petechial haemorrhages and telangiectatic areas. Quadrantic biopsies were taken and the histology was reported: there is telangiectatic dilation and congestion of the submucosal vessels. The submucosa is oedematous and there are extravasated red cells beneath the epithelium. The submucosal fibroblasts are atypical in places. The changes are reminiscent of the appearances following irradiation. No evidence of malignancy (Fig.).

The bleeding stopped spontaneously.

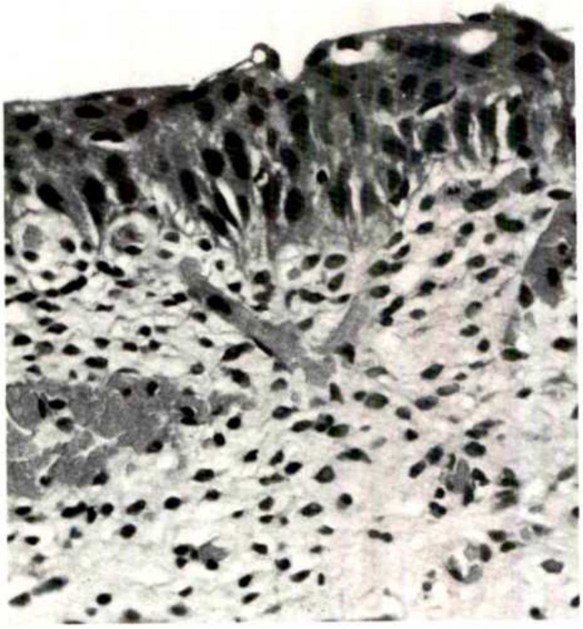

Fig. Photomicrograph showing telangiectasia, erythrocyte extravasation and submucosal oedema (×60).

Comment

Busulphan is an alkylating agent with similar radio-mimetic, antineoplastic and immuno-suppressive effects to cyclophosphamide. Whereas the latter is known to cause a troublesome haemorrhagic cystitis, no similar lesion has been seen with long-term busulphan. However Koss *et al.* (1965) reported significant cancer-mimetic cellular abnormalities in the epithelium of the lower urinary tract and these can cause difficulties for the cytologist. Busulphan has also been implicated in the induction of tumours of the breast, cervix and vulva (Nelson and Andrews, 1964; Koss *et al.*, 1965). We are now seeing cases of cyclophosphamide-induced bladder tumours (Ansell and Castro, 1975) and it may be that we shall be seeing the same thing with patients on long-term busulphan. Even patients with leukaemia may now survive long enough to experience the carcinogenic effects of the alkylating agents and it might be prudent to advocate cystoscopy on all patients taking these drugs for long periods.

Acknowledgement

I wish to thank Mr L. E. Edwards for permission to report this case.

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British Journal of Urology (1978), **50**, 209

Case Reports

Foreign Body Migrating to the Kidney

Case Report

A 48-year-old black male presented with left pyelonephritis. Plain film of the abdomen (Fig.) revealed a left staghorn calculus and urine culture was positive for Klebsiella. On excretory urography there was some left hydronephrosis and significant cortical thinning. Left pyelolithotomy was performed, and only moderate perirenal inflammation was found. The calculus was soft and friable, and the main fragment was formed about a wooden toothpick. Recovery was uneventful, subsequent urine cultures were sterile, and plain film at 6 months showed no recurrent calculi. The patient denied swallowing a toothpick or introducing one into the urethra.

Comment

Most renal foreign bodies result from traumatic injury. Nineteen cases have been reported in which the mode of entry was thought to be the gastrointestinal tract; approximately half were associated with calculi and only 4 of these occurred on the left. Two cases of perirenal abscess associated with a foreign body have been reported in which the kidney was uninvolved. In 7, entry was thought to be by retrograde migration from the urethra (Osmond, 1953; Baird and Spence, 1968; Chowdhury and Higgins, 1972). We believe that our case may represent another example of retrograde migration, as the perirenal inflammatory response was insufficient to suggest colonic perforation.

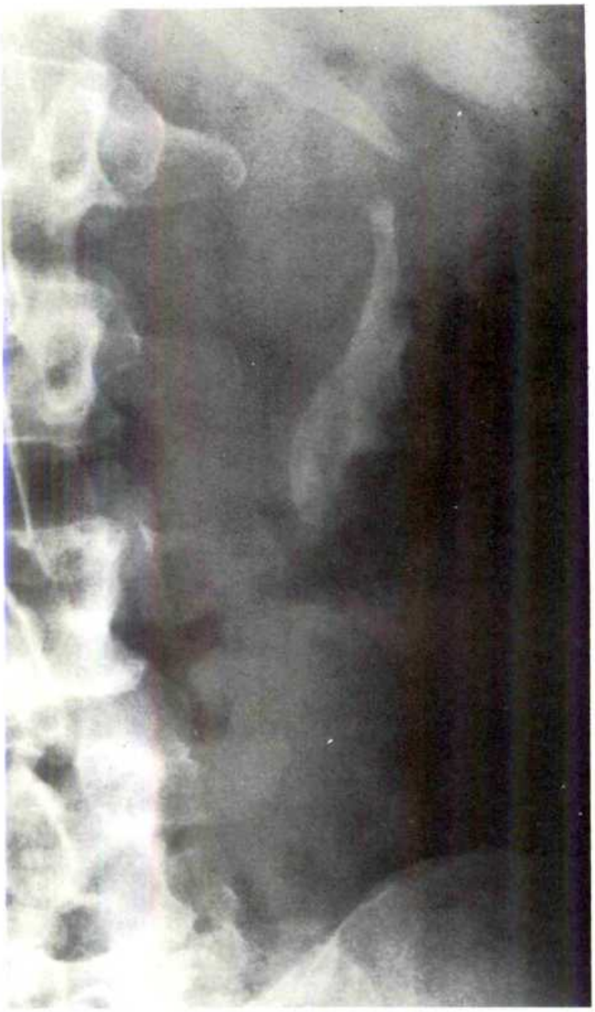

Fig.

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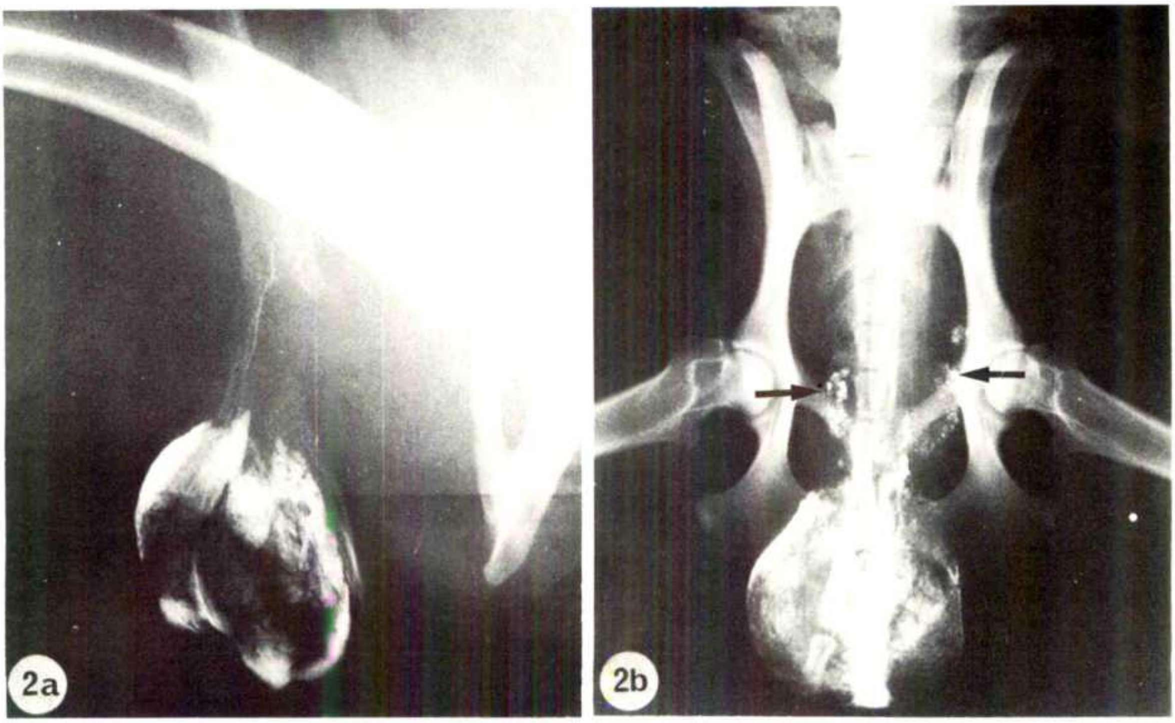

Fig. 2 Direct scrotal lymphography. (a) Lymphangiographic phase. (b) Lymphadenic phase (arrows indicate inguinal lymph nodes).

al., 1962; Rodriguez Sica and Sica, 1963) and since then the regional lymph nodes of various organs such as the lip, tonsil, tongue, prostate, testicle and rectum have been demonstrated Beales *et al.*, 1971; Gilbert and Lee, 1973; McCullough, 1975).

Direct intratissue lymphography is easily performed and does not require any special apparatus; it has the advantage that it is a simple way to show the regional lymph nodes of an area. In the present study and in the report by Stern and Doris (1967) direct testicular lymphography demonstrated more glands than by the more complicated pedal lymphography.

Failure to visualise the lymphatic channels of the vulva as well as a small number of glands in both the vulva and scrotum was mainly due to the rather viscous medium. Although a water soluble contrast medium, such as Hypaque, is better for demonstrating lymphatic channels, we preferred Lipiodol for this study because it remains for a longer period in the lymph nodes.

Intratissue lymphography might prove an easy and accurate method for the demonstration of metastatic deposits in humans. Perhaps the development of a soluble, thinner contrast medium would be more efficient for the visualisation of the regional lymph nodes and work in progress is directed towards this.

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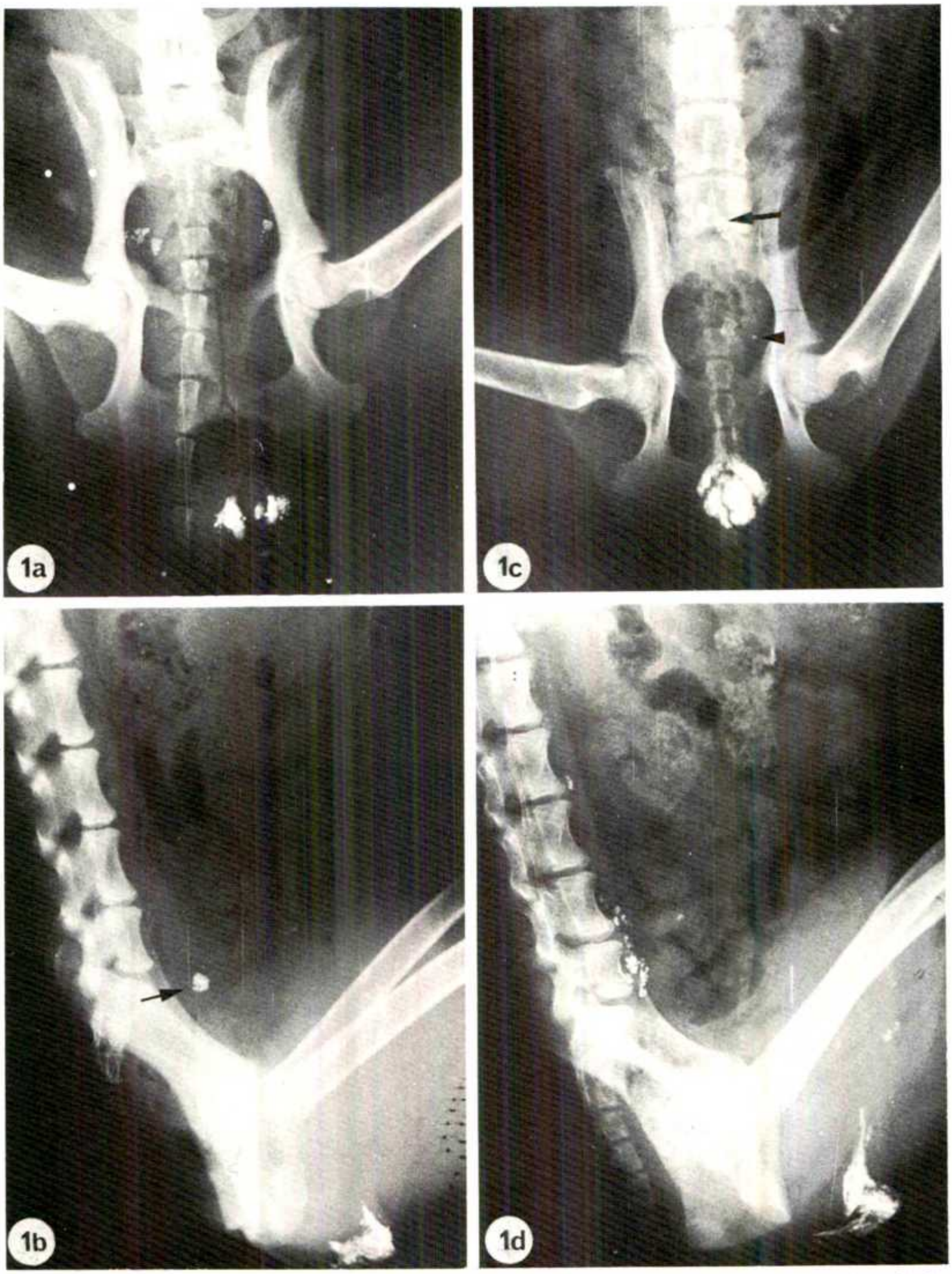

Fig. 1 Direct intratissue vulval lymphography (lymphadenic phase). (a) Bilateral inguinal nodes. (b) Internal iliac node (arrow). (c) Left inguinal node (arrow head) and common iliac nodes (arrow). (d) Common iliac and paraortic nodes.

British Journal of Urology (1978), **50**, 205-208

Visualisation of the Lymphatics of the Vulva and Scrotum by Direct Intratissue Injection of the Dye

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Summary—Visualisation of the regional lymph nodes of the vulva and scrotum was obtained in 12 dogs (6 females and 6 males) by direct intratissue injection of Lipiodol Ultra Fluid. The advantages as well as the potential applications of the method in humans are discussed.

Since the publications by Rodriguez Sica and Sica (1963) and Sica and Rodriguez Sica (1963), demonstrating the regional lymph nodes of various organs by direct injection of the dye into these organs, other investigators have reported their experience using a similar technique (Stern and Doris, 1967; Beales *et al.*, 1971; Gilbert and Lee, 1973; McCullough, 1975). This communication reports our results of direct intratissue lymphholography in the vulva and scrotum of dogs.

Material and Methods

Twelve dogs, 6 female and 6 male, weighing between 14 and 19 kg were studied by direct vulval and scrotal lymphography.

All the examinations were performed under general anaesthesia. An anaesthetic was used (Nembutal intravenously 0.5 ml/kg) both for the immediate or lymphangiographic and for the later (after 24 h) or lymphadenic phase.

The contrast medium of Lipiodol Ultra Fluid was centrifuged and warmed to 50°C and given in 1 dose of 1 ml for both examinations.

The injection in the vulva was done in multiple sites in the mucosa and submucosa, and in the sheath of the scrotum in 4 different sites.

Radiographs were taken at 5, 30, 60 and 120 min and at 24 h after the injection.

Results

Vulva

The examination failed to demonstrate the tiny lymphatic channels of the vulva but by 24 h there was evidence of opacification of some of the regional lymph nodes in all experiments (Fig. 1); in dog II the nodes appeared to belong to the internal iliac group.

Table 1 shows the number of opacified lymph nodes in each animal as well as the group to which they belong. The location of each gland was defined more accurately in some of the animals by a combination with angiography.

Scrotum

In these studies both lymphatic channels and lymph nodes were demonstrated (Fig. 2). The lymphatic channels were very fine in calibre and varied from 3 to 6 in number; all of the lymph nodes belonged to the inguinal group.

Discussion

Since its introduction by Kinmonth *et al.* (1955) pedal lymphography has gained wide acceptance in the investigation of diseases of the lymphatic system. Although it is a relatively easy procedure it is time consuming and requires a small operation which is rather unpleasant for many patients.

A decade ago, successful attempts were made to visualise the lymphatics by direct intratissue injection of the contrast medium (Di Matteo *et*

Table 1

Experiment No.	*Lymph nodes*	*Number*
I	External iliac lumbar, inguinal	5
II	Internal iliac	1
III	Inguinal	4
IV	Inguinal	3
V	Inguinal	4
VI	External iliac	2

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not clear. Helmstein intravesical distension therapy has been utilised to treat unstable detrusor dysfunction with some success (Dunn *et al.*, 1974). In the patients herein reported, urethral relaxation occurred and was not accompanied initially by a detrusor contraction. Ultimately, however, one-third of patients did regain contractile bladder responses to filling which continued to be fully coordinated with urethral relaxation, but totally non-volitional. Anticholinergic treatment in these latter patients clearly increased vesical capacity and delayed micturition responses, but when they occurred they continued to be sudden and uncontrolled, suggesting that the primary disability involved a loss of cerebral appreciation of bladder events. Two of these patients were subjected to deliberate overdistension and again lost contractile detrusor responses. Bradley and co-workers (Bradley *et al.*, 1974) have suggested that long sensory fibres originating in the bladder bypass the sacral micturition centre to synapse directly in the brain stem. On clinical grounds there is some evidence that the neural pathways (Nathan and Smith, 1958) for reflex vesical function and cognitive appreciation of vesical events are separate. This concept has profound clinical implications in that it may well be possible to injure selectively pathways subserving cognitive function without affecting those subserving reflex function. Sehn (1976) has shown, in rabbits, degeneration of fine neural fibrils in the bladder fundus after overdistension and it is possible that these are sensory fibres and that a peripheral sensory neurological injury could result in escape of the detrusor reflex from cerebral control.

This particular group of patients demonstrates urethral behaviour which is compatible with that seen in reflex micturition, in spite of the lack of contractile bladder response. The findings strongly suggest that complete urethral relaxation is not dependent on detrusor fibres pulling open the bladder neck and further that persistent urethral closure at extremes of bladder filling may result from failure of the micturition reflex, as well as urethral obstruction. There is no ready explanation as to why some of these patients recovered detrusor contractile responses and some did not. It is possible that overdistension in some patients resulted in failure of the bladder musculature to respond to parasympathetic discharge and this may be related to the severity and chronicity of the prior overdistension.

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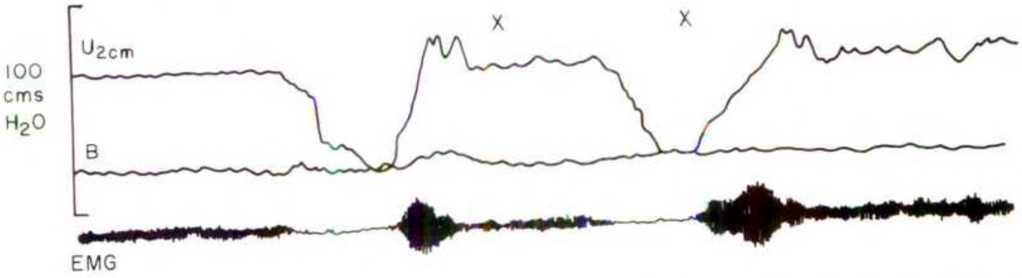
Fig. 3a



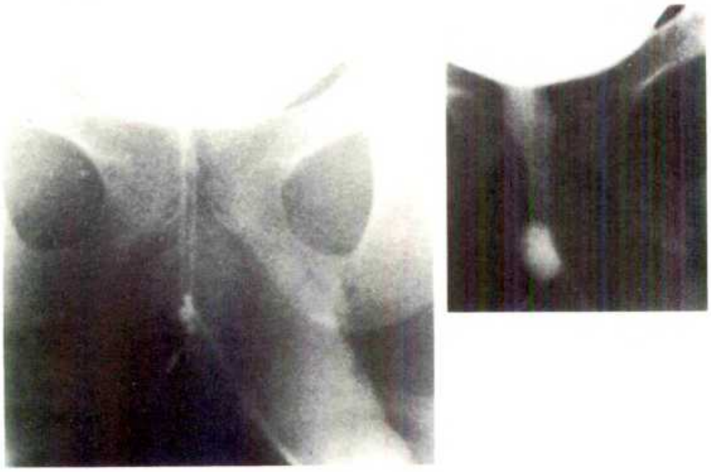


Fig. 3b Urethral (U) and bladder (B) pressures and external sphincter EMG showing 3 periods of total loss of positive urethral closing pressure provoked by bladder filling. Radiographs taken at point X above the urethral tracing show a closed urethra (left side) and an open urethra (right side) which occurred at the time of loss of urethral closing pressure.

raphy in such patients demonstrates closure of the internal urinary meatus (McGuire and Wagner, 1977). Moreover, urinary loss occurs as a result of an increase in intravesical pressure which overcomes intraurethral pressure. This is due to the intrinsic bladder tonic response to filling and occurs with no loss of urethral closing pressure. In contrast, the patients herein reported showed complete loss of urethral closure both by pressure measurements and on urethrography at discrete intervals. These periods were not associated with any change in intravesical pressure. The intravesical volume required to induce urethral relaxation was relatively small, and further filling to 600 ml did not result in detrusor activity. It might be argued that with total skeletal muscular relaxation the weight of the bladder contents could force the urethra to open. However, this does not occur in patients upright after complete sacral rhizotomy, nor does it occur in patients with lesions of the sacral cord resulting in loss of pelvic floor skeletal muscular activity (Abel *et al.*, 1974). Moreover, this intermittent urethral relaxation was observed in 70% of patients in the supine, as well as the standing position. Since intravesical pressures did not vary, but intraurethral pressure was completely lost, and since it is clear that loss of skeletal muscular function alone does not change intraurethral pressure or effective urethral length, it seems reasonable to conclude that both urethral, smooth and skeletal muscular relaxation occurred.

In the cat, intradural stimulation of the distal stump of the S_3 ventral root, severed from central neural pathways, induces loss of urethral smooth muscular closure. This response therefore does not appear to be due to central inhibition of sympathetic tonus (McGuire *et al.*, 1977). The relaxation response can be blocked with propanolol, a beta blocking agent, but not with phenylephrine, an alpha agonist. These findings strongly suggest that urethral smooth muscular relaxation engendered by bladder filling is a response to parasympathetic discharge, which ultimately involves beta receptor excitation. Similar urethral relaxation responses have been reported in man, and in primates, following sacral root stimulation (Torrens, 1976; Brindley, 1976). The ability to block urethral relaxation in this group of patients with an anticholinergic agent gives some clinical support to this hypothesis.

The significance of the historical evidence of vesical overdistension in each of these patients is

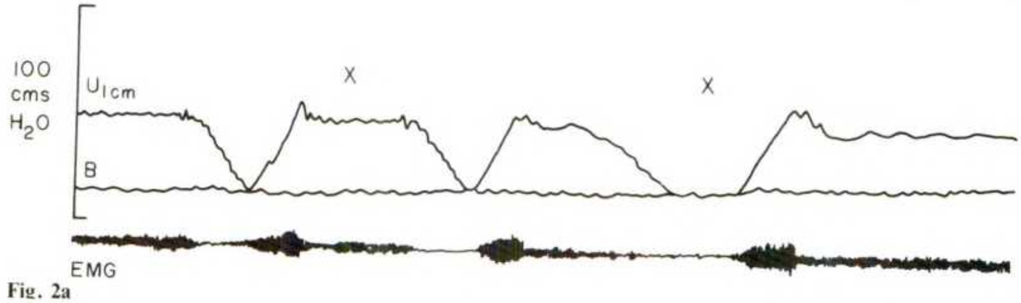


Fig. 2a

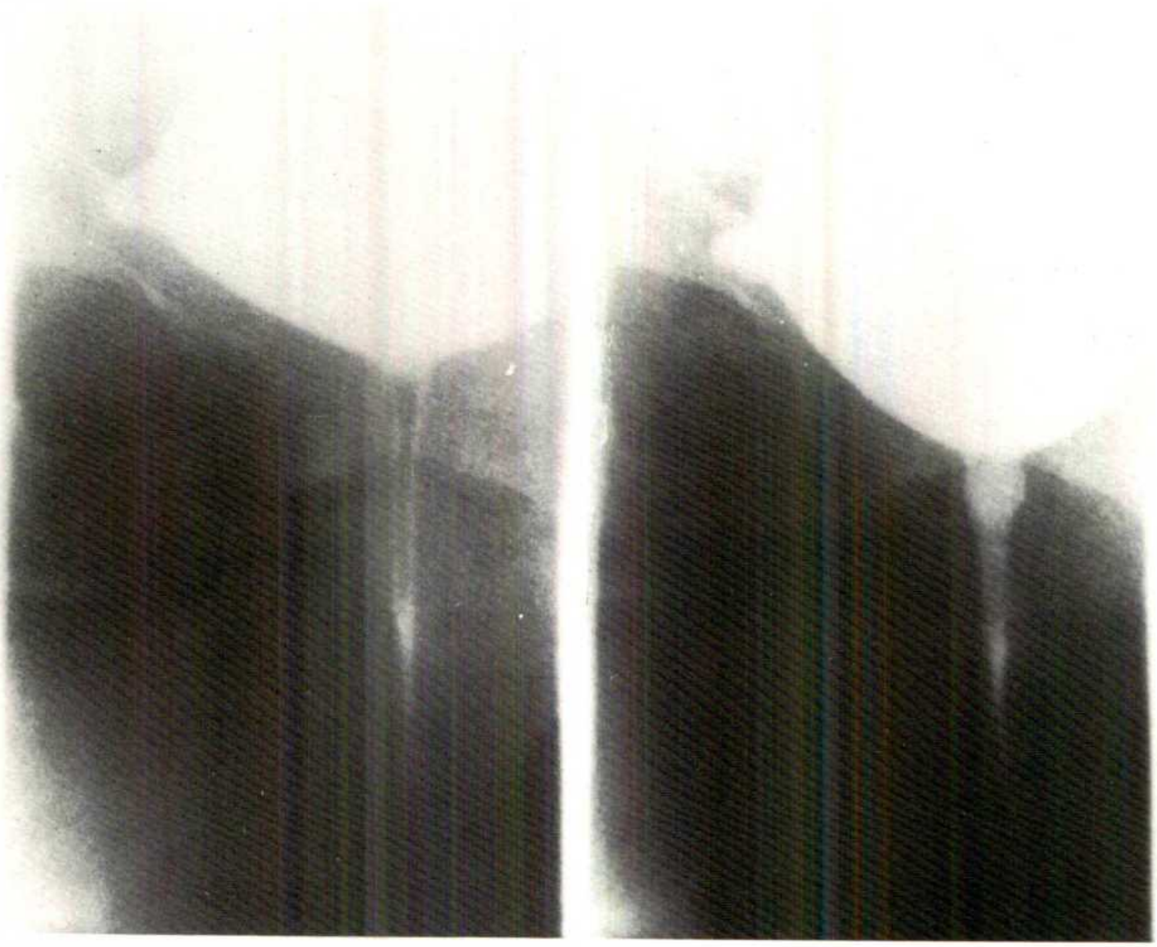


Fig. 2b Simultaneous, urethral (U) and bladder (B) pressures with external sphincter EMG during bladder filling showing 2 episodes of sudden loss in urethral pressure with suppression of EMG activity and a widely patent urethra seen on the right-hand radiograph, with visible urinary loss. The left-hand radiograph shows a closed urethra. Time of radiographic exposures shown by X above the urethral pressure tracing.

vity cease prior to voiding. However, there is considerable debate surrounding the precise events which result in opening of the "internal" or smooth muscular sphincter. It has been shown that smooth muscular closure of the urethra is exerted over the entire active urethra including the area most closely associated with striated muscular activity (Downie and Awad, 1976). Urethral profile determinations in patients following complete sacral rhizotomy are not markedly different from normal despite a decrease in peak profile amplitude associated with denervation of skeletal muscle. Upright cystog-

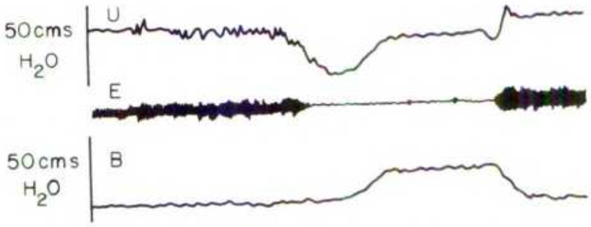


Fig. 1a (a) Bladder (B) and urethral (U) pressure and external sphincter EMG (E) during volitional voiding in a 20-year-old woman. Urethral pressure falls prior to the detrusor pressure rise. During flow, both bladder and urethral pressures are equal and there is electrical silence from the perineal floor. (b) The urethra opens visibly on the radiograph taken at the point on the tracing when urethral pressure decreases just prior to the detrusor pressure increase.

patient then developed urinary incontinence, which was however, associated with a 100 to 400 ml residual urine volume. Urodynamic investigation during bladder filling showed repeated episodes consisting of a sudden loss of urethral pressure which began at approximately 75 ml bladder content. At this time, a widely patent urethra was visible fluoroscopically. The loss of urethral closing pressure was associated with cessation of external sphincter EMG activity (Fig. 2). There was no change in intravesical pressure despite total loss of positive urethral closing pressure. Although urinary loss was recognised by the patient when it occurred, she was unaware of any bladder sensation at the time of the loss of urethral closing pressure which preceded it. Once urinary loss was appreciated there was a sudden increase in EMG activity accompanied by a sharp rise in intraurethral pressure, and urine flow ceased. These events, which occurred repeatedly during bladder filling, ceased entirely after treatment with Ditropan (oxybutinin 25 mg/day).

Case 2. A 41-year-old female developed urinary retention following a back injury and was evaluated because of persistent urinary retention associated with intermittent urinary incontinence. Urodynamic investigation showed sudden loss of urethral closing pressure accompanied by electrical silence from the perineal floor and subsequent urinary loss. There was no measurable detrusor activity (Fig. 3). The urethra was seen to open fluoroscopically and when urinary loss was appreciated by the patient, EMG activity suddenly increased with a consequent rise in urethral pressure.

Eleven other patients, including 4 males, have been encountered with exactly the same urodynamic findings, all with a history of prior severe urinary retention. Four patients followed for 2 years ultimately recovered detrusor reflex responses. However, the recovery of detrusor reflex responses was associated with worsening of incontinence since patients continued to lack sensory appreciation of both bladder filling and detrusor activity. They were aware only of intermittent gross urinary loss. The remainder of the patients have not regained detrusor responses and have been managed with intermittent catheterisation and treatment with anticholinergic agents.

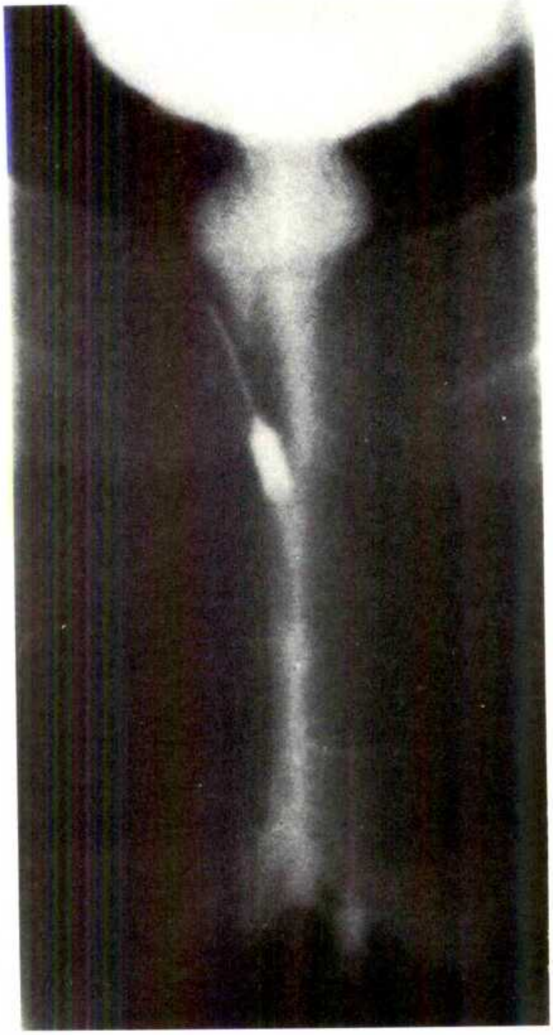


Fig. 1b

Discussion

Urodynamic findings in these patients showed total urethral relaxation, associated with perineal floor electrical silence, and a profound fall in urethral closing pressure. These events occurred entirely without cognitive appreciation until urinary loss was appreciated. It has been previously demonstrated (Tanagho and Miller, 1970) that striated urethral sphincter and pelvic floor muscular acti-

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Reflex Urethral Instability

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Summary—Eleven patients with incontinence and large post-voiding residual urine volumes have been studied with a urodynamic technique. Results indicate that reflex urethral relaxation was responsible for urinary incontinence. A probably relationship of this syndrome to bladder overdistension is suggested by ancillary evidence.

Evidence from animal studies indicates that urethral skeletal and smooth muscle relaxation occur as part of the detrusor reflex response (McGuire, 1976). Urodynamic studies in pathological states suggest that a similar detrusor-sphincteric coordination exists in man (McGuire *et al.*, 1976).

We have recently encountered 14 patients who complained of urinary incontinence in association with a large post-voiding residual urine volume. All these patients had suffered a prior episode of bladder overdistension and appeared to manifest overflow incontinence due to myogenic bladder decompensation. However, urodynamic evaluation showed sudden, profound urethral relaxation with total loss of positive urethral closing pressure at intervals apparently provoked by bladder filling without a corresponding increase in intravesical pressure. Involuntary urinary loss occurred at the time of the fall in urethral closing pressure. Patients were aware of urinary loss when it occurred but were totally unaware of the preceding urethral pressure changes.

Methods

The urodynamic methodology involves the simultaneous recording of bladder and urethral resistance to flow (5 ml/min), induced by a double-barrelled syringe pump in 2 identical 8 Fr urethral profile catheters. Each catheter has a single lateral perfusion aperture located 8 cm from its distal tip. The perfusate is 20% diatrizoate (Hypaque) to permit fluoroscopic examination of the bladder and precise localisation of the perfusion aperture of the catheter used to record urethral pressures. An external sphincter EMG is recorded via 2 #30 Grass needle electrodes inserted into the area of the mid-urethra in females, and the prostatic apex in males.

Both catheters are inserted into the bladder *per urethram* and perfusion is begun. One catheter is withdrawn in 0.5 cm steps until its perfusion aperture has traversed the entire active urethra. The bladder is emptied, and the procedure is repeated in the upright position. Fluoroscopy demonstrates the precise anatomical area from which urethral pressures are recorded. Ten seconds are allowed at each centimetre withdrawal step for pressure equilibration. The urethral catheter is then repositioned so that its perfusion aperture is located in the area 1.5 to 2.0 cm from the vesical outlet, and gradual bladder filling is allowed to take place while bladder and urethral pressures and external sphincter EMG are recorded.

Volitional voiding in the upright position results in the following pressure and electrical events which are reproducible and virtually invariable. External sphincter EMG activity ceases, abruptly, or in a series of short periods of relaxation and contraction which are followed by electrical silence. Urethral pressure begins to fall with these changes, and the urethra can be seen (fluoroscopically) to open. Intravesical pressure then increases and flow is noted in the distal urethra when intravesical and intraurethral pressure become equal. This equality of pressure persists throughout flow (Figs. 1a and b). If the urinary flow is diverted from the urethra via a suprapubic tube, urethral pressure loss can be seen to persist throughout the period of detrusor activity.

Patients

Case 1. A 30-year-old female with a life-long history of infrequent voiding developed urinary retention following a surgical procedure. A period of chronic retention of 300 to 800 ml of urine ensued which was treated by urethral dilatation, internal urethrotomy, and finally limited transurethral resection of the bladder neck. The

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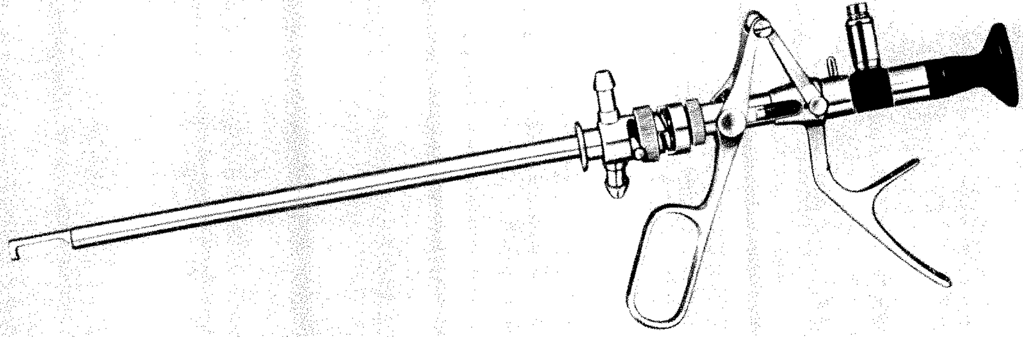

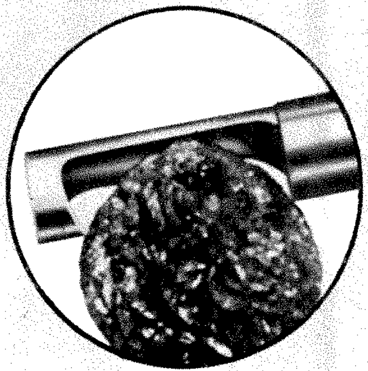

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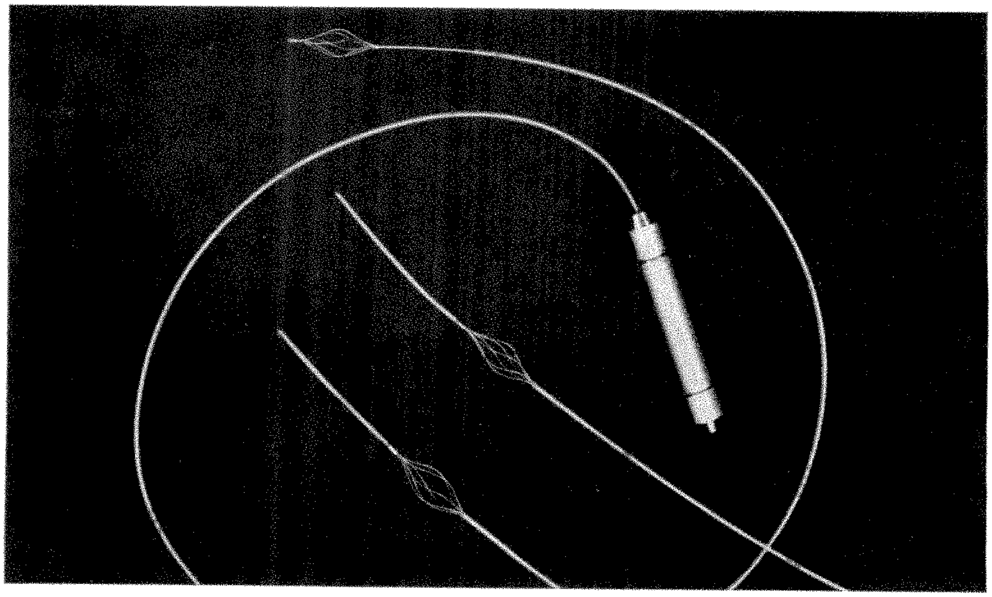

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Pyeloplasty in Infants and Children with Particular Reference to the Method of Drainage Post-operatively

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Summary—Sixty-three consecutive Anderson-Hynes pyeloplasties in infants and children have been reviewed with particular reference to any influence the method of drainage might have on the post-operative course and the final radiological result.

Extra-anastomotic drainage, usually with a sump drain, was used in 40 cases and pyelostomy drainage in 23 cases. Fewer post-operative complications were encountered in the former group.

The final radiological result was not influenced by the method of drainage except that, in patients under 2 years of age, those with pyelostomy drainage fared rather better.

It is concluded that (*a*) extra-anastomotic sump drainage is the method of choice following pyeloplasty in children over 2 years of age, and (*b*) in infants under 2 years of age pyelostomy drainage probably should be combined with a trans-anastomotic splint.

Intrinsic pelvi-ureteric obstruction is the commonest single cause of hydronephrosis in infants and children. Some form of pyeloplasty (Foley, 1937; Davis, 1943; Culp and De Weerd, 1954) is the conventional treatment for this condition and gives satisfactory results in most cases. Several authors have described their method of post-operative drainage but have not presented any statistical evidence to justify the policy they advocate. North American authorities suggest that in children it is essential that post-operative drainage should include a pyelostomy or nephrostomy with or without a transanastomotic splint (Culp *et al.*, 1962; Campbell and Harrison, 1970). In the United Kingdom probably the most widely practised pyeloplasty is that devised by Anderson and Hynes (Anderson and Hynes, 1949), and authorities with extensive experience of this procedure in infants and children (Williams and Karlaftis, 1966; Robson *et al.*, 1976; Johnston *et al.*, 1977), recommend that nephrostomy drainage with a trans-anastomotic splint should be used in view of the small calibre of the ureter. However, Anderson (Anderson, 1963), writing of his experience of 153 cases (mainly adults) specifically states that it is one of the principles of his procedure that "it should not be necessary to splint the anastomosis nor to drain the kidney".

In the Sheffield Children's Hospital no one policy of drainage after pyeloplasty has been followed, and we have therefore reviewed our more recent cases in an attempt to discover whether the method of drainage has any bearing on the post-operative complications and the late radiological findings.

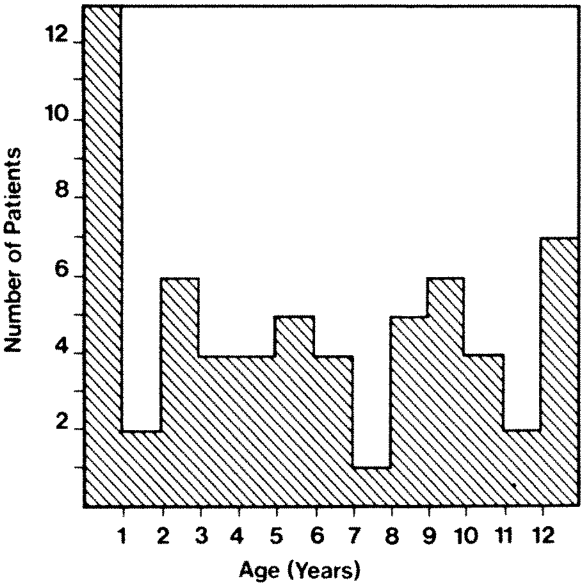

Fig. 1 Age of patients at operation.

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Table 1 Symptomatology

	No. of patients
Renal pain	28
Non-specific abdominal pain	6
Urinary tract infection	11
Haematuria	4
Vomiting	5
Renal mass	2
None (routine investigation of tracheo-oesaphageal fistula)	1

Patients

Fifty-seven patients had an Anderson-Hynes pyeloplasty performed for intrinsic pelviureteric obstruction in the years 1969 to 1975 inclusive. Thirty-eight patients were male and 19 female. In 32 instances the left kidney was involved and in 19 the right; 6 patients had bilateral disease, so that 63 pyeloplasties were performed in all.

The age of the patients at operation (Fig. 1) shows a peak in the early months of life. This is partly due to the fact that whereas all babies with pelviureteric obstruction would be referred to the neonatal surgical unit at Sheffield, many older children with the same condition would be dealt with at peripheral hospitals.

Non-specific abdominal pain was an uncommon mode of presentation (Table 1) and nearly all children old enough to give any kind of description of their symptoms clearly located their pain to the renal area. The less specific symptoms were seen almost exclusively in children under 2 years of age. Physical signs were infrequent, only 5 patients, all under 2 years of age, having a palpably enlarged kidney. Hypertension was recorded in only 1 patient, who also had pyelonephritic scarring of the opposite kidney as a result of vesico-ureteric reflux. Twenty-four patients (40%) had a documented urinary tract infection pre-operatively (*E. coli* 18, *Proteus* 5, *S. aureus* 1). However, a urinary tract infection was found in 11 (85%) patients presenting at less than 2 years of age.

Associated genito-urinary tract abnormalities were found in 6 patients (contralateral vesico-ureteric reflux 3, ipsilateral lower ureteric obstruction 2, ipsilateral renal calculi 1). Associated ipsilateral lower ureteric obstruction can easily lead to diagnostic difficulties: in 1 patient the condition was suspected when a dilated ureter was found at operation and the distal obstruction confirmed by a pre-operative antegrade pyelogram, but in the other patient the condition was only discovered on the post-operative IVP. In general, however, the diagnosis was seldom a problem and an IVP gave adequate information in 49 cases. Retrograde or antegrade pyelography was required in 8 cases where the function in the affected kidney was exceptionally poor.

Operative Technique

Although the operations were carried out by a total of 8 surgeons, of whom only 3 performed more than 10, the technique used was essentially the same in all cases. The approach to the renal pelvis was anterior and extraperitoneal. Aberrant lower polar vessels were found in 11 instances, but were not thought to be the cause of the obstruction in any. The method of resection and re-anastomosis was basically that described by Anderson and Hynes (Anderson and Hynes, 1949). Except in 3 neonatal cases where 5/0 Dexon$^{(R)}$ (Davis and Geck Ltd) was used, the suture material was 4/0 Collagen$^{(R)}$ (Ethicon Ltd) run as a continuous suture throughout.

Post-operative Drainage

This depended on the individual surgeon's preference. The 2 basic methods were (1) a pyelostomy using a De Pezzer catheter *without* a transanastomotic splint, and (2) simple extra-anastomotic (tissue) drainage of the renal bed, usually using a Shirley Sump drain (supplied by H. W. Andersen Products, New York). Prophylactic antibiotics were not administered to either group.

When a pyelostomy was employed, urine was allowed to drain through it for 48 h post-operatively, and the urine was then encouraged to pass through the anastomosis by clamping the pyelostomy for increasing periods of time. If this caused renal pain or urine drained round the catheter, free drainage was recommenced for a further 48 h, and then a further attempt was made at intermittent clamping. The pyelostomy was not removed until satisfactory drainage of urine through the anastomosis had been achieved; this was usually confirmed radiologically by injecting contrast material through the pyelostomy catheter.

When a tissue drain was used, this was removed 24 h after any leak of urine through it had ceased. Although the Shirley Sump drain was designed

Table 2 Post-operative Course and Complications

(*a*) Timing of removal of drains (days post-operatively)		
	Pyelostomy drains	Tissue drains
	Range 4-42 days	Range 3-12 days
	Average overall 16.0 days	Average overall 6.1 days
	(Patients <2 yrs, 21.4 days) (Patients >2 yrs, 12.2 days)	(Patients <2 yrs, 7.8 days) (Patients >2 yrs, 5.8 days)
(*b*) Complications		
	Pyelostomy drains	*Tissue drains*
None	7	33
Wound infection	5	6
Urinary infection	15	3
(*c*) Length of post-operative stay in hospital		
	Pyelostomy drains	Tissue drains
	Range 12-75 days	Range 7-23 days
	Average overall 24.8 days	Average overall 11.1 days
	(Patients <2 yrs, 31.3 days) (Patients >2 yrs, 19.8 days)	(Patients <2 yrs, 13.5 days) (Patients >2 yrs, 10.4 days)

for use with suction, in this series these drains were left on free drainage only.

Pyelostomy drainage was used for 23 operations (10 in patients under 2 years of age) and tissue drains for 40 operations (5 in patients under 2 years of age). Of these 33 were Shirley Sump drains, and 7 of other types (3 corrugated, 2 suction, 2 tube).

Post-operative Course and Complications

With tissue drains leakage of urine through the drain was minimal in most cases, and occurred in measurable amounts in only 13 instances. It was therefore usually possible to remove these drains in the early post-operative period (Table 2a). By contrast, although it was the intention to remove pyelostomy drains some 7 to 10 days post-operatively, this was rarely achieved (Table 2a). In several cases it was shown radiologically that from 5 to 10 days post-operatively very little contrast material could be persuaded to pass through the anastomosis. This state of affairs resolved within 21 days post-operatively in all but 2 cases, both of which required retrograde catheterisation of the anastomosis before the pyelostomy could be removed.

Because pyelostomy drains lay within the renal pelvis and because they often could not be removed in the early post-operative period, the incidence of urinary tract and wound infections was greater with this type of drainage than when tissue drains were used (Table 2b).

The combined effects of prolonged urinary drainage with pyelostomies, and the consequent complications, are reflected in the length of stay in hospital post-operatively (Table 2c).

Long Term Clinical and Radiological Results

In this series no patient complained of post-operative renal pain no matter how indifferent the radiological result. Only 1 patient suffered from recurrent urinary tract infections post-operatively; that patient had pyelostomy drainage.

The functional result of a pyeloplasty is difficult to assess; although computerised isotope renography may be of value (Kathel, 1972), the only method readily available is to compare the pre- and post-operative IVP. This method, however, gives an anatomical rather than a functional assessment of the result, and is also highly susceptible to observer error. In an attempt to minimise the latter, each author assessed the radiographs independently, and where there was disagreement, which was surprisingly seldom and never to a marked degree, the issue was decided on the toss of a coin. The radiographs reviewed were the pre-operative IVP and the first post-operative IVP provided this latter had been performed at least 3 months post-operatively; we found that IVPs performed earlier than this sometimes showed a poor result which improved on later radiographs, whereas there was rarely any marked improvement 3 months or more after operation.

The radiographs of 10 patients were mislaid or destroyed, so that the total number of pyeloplasties we could assess radiologically, including 3 patients with bilateral disease, was 53.

The degree of hydronephrosis was classified into 5 grades:

Grade I	Pelvic dilatation, normal calices, normal renal cortex.
Grade II	Pelvic dilatation, mild caliceal dilatation, normal renal cortex.
Grade III	Pelvic dilatation, marked dilatation of calices, normal renal cortex.
Grade IV	Pelvic dilatation, marked caliceal dilatation, thinning of renal cortex.
Grade V	Pelvic dilatation, gross dilatation of calices, marked thinning of renal cortex.

The pre-operative assessments are shown in Table 3. The post-operative radiographs were similarly assessed, with the addition of "half a

Table 3 Pre-operative Assessment of Hydronephrosis

	Overall	*Pyelostomy*	*Tissue drains*
Grade I	6	2	4
Grade II	6	2	4
Grade III	17	8	9
Grade IV	11	5	6
Grade V	13	4	9

grade" of improvement when the ureter could be seen on the post-operative, but not the pre-operative, IVP. The radiological result of the operation was calculated from the formula

$$\frac{\text{Grade Hydronephrosis Pre-op—Grade Hydronephrosis Post-op}}{\text{Grade Hydronephrosis Pre-op}} \times 100$$

and the percentage obtained placed in 1 of 5 categories:

66% + = Good Result
33-65% = Satisfactory Result
1-32% = Fair Result
0 = No Change
Negative = Worse

Overall, the radiological result was not influenced by whether pyelostomy or tissue drainage was used (Fig. 2). However, in cases under 2 years of age at operation, of 10 with pyelostomy drainage 7 showed improved appearances post-operatively (*i.e.* a fair to good result), whereas of the 5 with tissue drainage only 2 showed improvement, and then only a fair result. Conversely, in children over 2 years of age, the results with tissue drainage were marginally better than those with pyelostomy drainage.

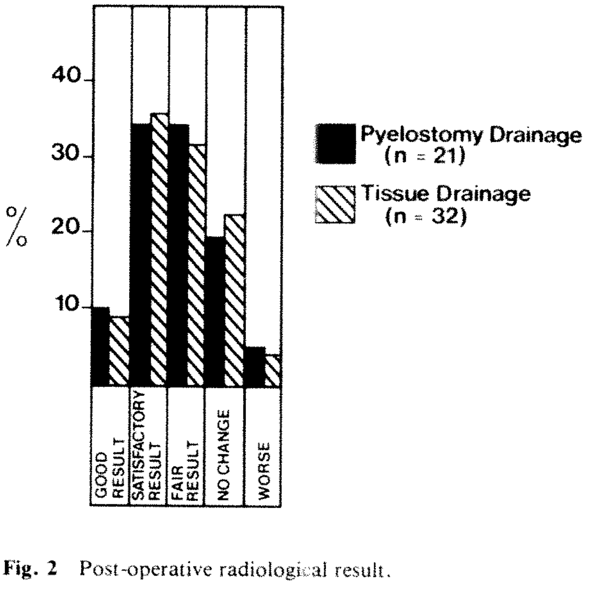

Fig. 2 Post-operative radiological result.

Discussion

When Anderson (Anderson, 1963) commented that he did not drain the renal pelvis or use a trans-anastomotic splint, it was his belief that patency of the anastomosis was best ensured by encouraging urine to pass through it *ab initio*. However, it has been feared that in infants and children only a little oedema at the anastomosis will completely occlude the lumen of the ureter, and that therefore drainage of the renal pelvis plus a trans-anastomotic splint is essential. We have presented the results with a compromise form of management, that is pyelostomy drainage without a trans-anastomotic splint. The rationale of this method is to allow free drainage of the kidney and early healing of the anastomosis during the period when post-operative oedema might compromise the lumen of the ureter at the lower end of the anastomosis. It may be objected that this is an inherently unsatisfactory compromise, in that if urine is being drained entirely by a pyelostomy in the immediate post-operative period, then the 2 sides of the anastomosis may fall together and become united by a film of fibrin. Our analysis suggests that this does indeed occur as evidenced firstly by the difficulty in persuading urine to pass through the anastomosis after leaving the pyelostomy on free drainage for as little as 2 days post-operatively, and secondly by the 2 patients who required retrograde catheterisation of the anastomosis to open it up long after any post-operative oedema should have subsided. We have therefore come to the conclusion that this method of management is unsatisfactory.

In this series tissue drainage, as recommended by Anderson, in addition to its relative simplicity was superior in the post-operative period and gave equally good long-term results in the series as a whole. We have no experience with the use of trans-anastomotic splints, but although comparison of our results with those of other series where these were used (*e.g.* Johnston *et al.*, 1977) is difficult, we doubt if the use of such splints would have given any better results in children over 2 years of age.

However, if tissue drainage is to be used it is with 2 provisos. Firstly, the drain must be efficient. If it is not, then any leak of urine will pool in the perinephric space, leading to infection and healing with excessive fibrosis. In this series the Shirley Sump drain proved to be most efficient.

The second proviso relates to the age of the patient and hence the calibre of the ureter. In this series, although the numbers were small, the results with tissue drainage in children under 2 years of age left much to be desired. It may be that in infants there is a place for trans-anastomotic splintage; this possibility would seem to merit a controlled prospective trial.

Acknowledgements

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Prediction of Renal Recovery in Hydronephrotic Kidneys

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Summary—Urine produced by obstructed kidneys was analysed in 35 cases. In the absence of infection by urea splitting organisms, estimation of urinary pH of hydronephrotic kidneys was found to be a reliable method for determination of recovery potential.

After removal of obstruction, radiological recovery was almost complete when the pH was lower than 6.

Obstructed kidneys producing urine with a pH between 6-7.1 showed only partial radiological recovery after surgical correction.

All kidneys that showed no function on IV urography and those found at operation to possess only a very thin shell of cortex to justify nephrectomy were found to have urinary pH near 7.3 or more, implying inability of those kidneys to acidify urine.

Urinary specific gravity and sodium concentration of obstructed kidneys were not reliable in prediction of renal recovery.

The maximum period that a human kidney would stand complete obstruction and remain capable of recovery after release of that obstruction has not yet been clearly defined. Renal recovery after ureteric deligation has been reported to occur in kidneys that were obstructed for up to 69 days (Lewis and Pierce, 1962). At present operative treatment aims at preservation of obstructed kidneys when there is a reasonable degree of renal function demonstrated on intravenous urography. On the other hand, nephrectomy is performed when the kidney appears to be radiologically functionless and/or the cortex is found at operation to be reduced to a thin shell. Between these 2 extremes the surgeon may find difficulty in making a decision on the preservation of an obstructed kidney in unilateral cases. The present method commonly used of evaluation of renal function, *i.e.* IV urography, may sometimes be of no help in this context. There are scattered reports in the literature of kidneys that were declared functionless on IV urography, yet after removal of obstruction those kidneys recovered to a useful extent (Schulhof, 1937; Graham, 1962). It is in situations like this that the surgeon at present judges from the anatomical appearance of the kidney at operation whether to remove or preserve the hydronephrotic kidney.

The aim of this study is to investigate the physical and chemical properties of "hydronephrotic urine", to try to correlate the results with the renal function as determined radiologically by IV urography and anatomically by appearance at operation. It is hoped that this analysis may provide an objective method for assessment of renal function, prediction of recovery and planning of treatment of severely obstructed kidneys.

Materials and Methods

This prospective study was performed on 35 randomly selected patients admitted to Soba University Hospital in Khartoum with unilateral hydronephrosis due to different causes as listed in Table 1. The age of patients ranged from 6 to 50 years. There were 24 males and 11 females.

Table 1 Different Causes of Hydronephrosis and Sex Distribution

Cause	*Number of cases*		*Total*
	Males	*Females*	
Renal stone	10	2	12
Ureteric stone	10	8	18
Congenital hydronephrosis	2	–	2
Bilharzial ureteric stricture	1	1	2
Vesical diverticulum pressing on ureter	1	–	1
Total	24	11	35

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All patients had IV urography, urine culture, serum potassium and blood urea estimation to exclude renal failure and hyperkalaemia prior to the operation.

In 20 out of the 35 patients, 30 ml of urine was collected at operation for comparison purposes, by a ureteric catheter from the contralateral normal kidney, consent of the patient having been obtained beforehand. All patients were put on a diet poor in alkaline ash for 3 days prior to the operation, which was done under general anaesthesia. Ten millilitres of this urine was sent for culture and 20 ml was used for estimation of pH, sodium concentration and specific gravity. The pH was estimated in the theatre, using a pH meter; sodium concentration was estimated by the flame photometer and the specific gravity by the hygrometer. In the whole group of 35 patients, 30 ml of urine was also aspirated at operation by a wide bore needle from the hydronephrotic kidney before removal of the obstruction. Of this, 10 ml was sent for culture and the rest was again used in estimation of pH, sodium concentration and specific gravity. All patients had an IV urogram 2 months after the correction of the obstruction to determine the degree of recovery. Recovery was thus only judged radiologically in this series. It was considered complete when the length of the kidney, cortical thickness, ability to concentrate the dye and pelvicalyceal configuration returned to normal in comparison to the contralateral sound kidney. On the other hand, recovery was taken as partial when the post-operative IV urography revealed disparity between both sides in length, cortical thickness, pelvicalyceal configuration or dye concentration.

Only these parameters were used to assess the degree of renal damage and recovery and no attempt was made to study renal function by other methods, such as creatinine clearance. The radiological findings and anatomical appearance of the kidney at operation were both correlated with the results of the analysis of the "hydronephrotic urine".

Table 2 Shows Urinary pH on Hydronephrotic and Normal Sides, the Infecting Organism and Degree of Renal Recovery after Removal of Obstruction

Case No.	*Urine culture*	*pH on hydro-nephrotic side*	*pH on normal side*	*Degree of renal recovery*
1	Negative	8.4	5.2	Nephrectomy done
2	Negative	4.0	3.9	Complete
3	Negative	6.1	5.8	Partial
4	*Proteus*	7.0	5.8	Partial
5	Coliform	6.6	5.4	Partial
6	Negative	6.6	5.7	Partial
7	Coliform	6.2	5.0	Partial
8	Coliform	6.4	6.2	Partial
9	Negative	7.2	5.5	Nephrectomy done
10	Coliform	6.4	6.0	Nephrectomy done
11	Negative	6.2	5.9	Partial
12	*Pseudomonas*	6.6	5.6	Partial
13	Negative	7.0	6.1	Partial
14	Negative	6.0	5.8	Complete
15	Negative	6.0	5.4	Complete
16	Negative	6.8	5.8	Partial
17	*Klebsiella*	7.0	5.2	Partial
18	Negative	5.4	5.4	Complete
19	Coliform	7.1	4.6	Partial
20	Coliform	6.5	4.8	Partial
21	*Pyocyaneus*	5.2		Complete
22	*Pyocyaneus* + coliform	7.0		Partial
23	*E. coli*	7.0		Partial
24	Negative	6.7		Partial
25	*Klebsiella* + *Proteus*	7.6		Partial
26	*Pseudomonas*	6.2		Partial
27	Negative	7.6		No recovery
28	Negative	6.6		Complete
29	*E. coli*	5.3		Complete
30	Negative	6.5		Partial
31	*Pseudomonas*	7.0		Partial
32	Negative	6.3		Partial
33	*Proteus*	7.4		Partial
34	Negative	6.0		Complete
35	*E. coli*	6.3		Partial

N.B.: By partial recovery it is meant that concentration of dye and pelvicalyceal configuration on IV urography did not go back to normal after complete removal of obstruction.

Results

pH

Table 2 shows the pH of the urine of the obstructed kidneys and its correlation with radiological renal recovery. In 20 cases out of the whole group, the pH was compared with that of the urine of the contralateral normal kidney. Only in case 2 were the pH readings outside the normal physiological ranges. Otherwise pH was always higher on the side of hydronephrosis, except in case 18, where the patient presented very early with an acutely obstructed kidney, and a calculus obstructing the ureteric orifice was removed instrumentally. Presumably that transient obstruction did not affect the ability of the kidney to acidify urine. However, as can be seen later (Table 3), concentration of urine in that kidney was poor as indicated by the lower specific gravity in comparison with the other side.

In 8 cases the urine in the hydronephrotic kidney was infected. It is only when infection was caused by urea splitting organisms, *e.g.*

Table 3 Comparison between Specific Gravity of Urine in the Hydronephrotic Kidney and the Contralateral Sound Kidney in 20 Patients

Case No.	*Urine culture*	*Hydronephrotic kidney*	*Normal kidney*	*Degree of recovery*
1	Negative	1005	1018	Nephrectomy done
2	Negative	1006	1020	Complete
3	Negative	1016	1006	Partial
4	*Proteus*	1015	1002	Partial
5	Coliform	1030	1040	Partial
6	Negative	1001	1006	Partial
7	Coliform	1002	1022	Partial
8	Coliform	1002	1012	Partial
9	Negative	1020	1000	Nephrectomy done
10	Coliform	1008	1016	Nephrectomy done
11	Negative	1002	1012	Partial
12	*Pseudomonas*	1003	1010	Partial
13	Negative	1002	1010	Partial
14	Negative	1006	1010	Complete
15	Negative	1001	1010	Complete
16	Negative	1009	1010	Partial
17	*Klebsiella*	1006	1014	Partial
18	Negative	1008	1018	Complete
19	Coliform	1019	1007	Partial
20	Coliform	1028	1040	Partial

Proteus, that urinary pH did not correlate well with the severity of the obstruction and subsequent radiological recovery. Nephrectomy was done in cases 1 and 9, where the pH of the "hydronephrotic urine" was near 7.3 or higher. Both those kidneys were functionless on IV urography and judged useless at operation. However in case 10, although nephrectomy was also done because the kidney was pyonephrotic, the pH was 6.4. IV urography in that case showed a poor nephrogram.

It is probable that the kidney may have recovered to a useful degree if a nephrostomy had been done as it was still capable of acidifying its urine down to a pH of 6.4, in spite of infection by *Proteus* which is known to occur in alkaline urine. However, the validity of this statement could not be substantiated as the kidney was removed.

Radiological renal recovery as determined by IV urography 2 months after removal of obstruction was complete in 8 cases. In 7 (87.5%) of these, the urinary pH with obstruction was not higher than 6. In 23 cases, the recovery was partial and the urinary pH with obstruction was between 6 to 7.1, except in cases 25 and 33 and in both the pH was higher than 7.3, due to infection by *Proteus*. In case 27, urinary pH was 7.6 in the absence of infection and that particular kidney did not show any radiological recovery 2 months after removal of obstruction.

Specific Gravity

Table 3 shows a comparison between the specific gravity of urine in the obstructed and normal kidney in 20 cases. It was lower on the hydronephrotic side in 8 (73%) out of 11 cases with no infection and in 7 (77.7%) out of 9 cases with infection. The difference is not significant. There was no correlation between specific gravity, degree of obstruction and radiological recovery after removal of obstruction.

Sodium Concentration

Table 4 shows a comparison between the urinary sodium concentration of hydronephrotic and normal contralateral kidneys in 20 cases. The urine of hydronephrotic kidneys possessed a higher sodium concentration than the urine of

Table 4 Shows Comparison between Sodium Concentration in the Urine of the Hydronephrotic Kidney and the Normal Kidney in 20 Patients

Case No.	*Urine culture*	*Na concentration on hydronephrotic side meq/litre*	*Na concentration on normal side meq/litre*	*Renal recovery*
1	Negative	137	116	Nephrectomy done
2	Negative	88	76	Complete
3	Negative	113	70	Partial
4	*Proteus*	121	38	Partial
5	Coliform	59	52	Partial
6	Negative	78	76	Partial
7	Coliform	114	142	Partial
8	Coliform	100	92	Partial
9	Negative	103	15	Nephrectomy done
10	Coliform	90	186	Nephrectomy done
11	Negative	27	121	Partial
12	*Pseudomonas*	51	88	Partial
13	Negative	75	113	Partial
14	Negative	50	75	Complete
15	Negative	11	120	Complete
16	Negative	149	76	Partial
17	*Klebsiella*	64	120	Partial
18	Negative	73	41	Complete
19	Coliform	63	77	Partial
20	Coliform	56	108	Partial

the contralateral sound kidney in 7 (64%) out of 11 cases with no infection and in only 3 (33.3%) out of 9 cases with infection. There was no correlation between urinary sodium concentration, severity of obstruction and subsequent degree of radiological recovery.

Discussion

In hydronephrosis, the main kidney damage occurs in the collecting and distal tubules (Zimskind *et al.*, 1962; Berlyne, 1961). Studies on dog kidneys revealed that morphological recovery was complete after release of unilateral obstruction of 7 days' duration or less. Kidneys obstructed for longer periods showed only partial morphological recovery (Govan, 1961). However, radiological studies in obstructed canine kidneys disclosed that complete loss of function on IV urography occurs in kidneys obstructed for 2 weeks. After release of obstruction, radiological recovery was complete in kidneys that were obstructed for as long as 8 weeks (Zimskind *et al.*, 1962). Nevertheless, it is dangerous to apply these results obtained from experimental animals to obstructed human kidneys. Moreover, in clinical practice, it is almost impossible, with a few exceptions, to determine the exact duration of obstruction of a certain kidney. For those reasons the duration of obstruction as such cannot be used as a practical guide for prediction of recovery of obstructed kidneys. The urinary pH of those obstructed kidneys may be of help in this context. It was reported to be higher than that of the contralateral normal kidney, due to the impairment in the function of the distal renal tubules that occurs in association with hydronephrosis (Berlyne, 1961). In this series, recovery after release of obstruction occurred in all hydronephrotic kidneys with a urinary pH below 7.1 but it was only partial when the urinary pH was between 6 to 7.1.

Urinary pH of obstructed kidneys proved a reliable guide to subsequent recovery in cases of infected hydronephrosis, provided that the infecting organism was not of the urea splitting type. In Berlyne's report it was interesting to note that one of his cases with urinary pH of 7.04 never recovered kidney function, while other kidneys with urinary pH below 7 showed recovery after removal of obstruction. In that series, it was noteworthy to find that the single kidney with a urinary pH of 5.46 was the one out of the whole group capable of acidifying its urine normally down to a pH of 5.3 after correction of the obstruction. In our series, however, when nephrectomy was indicated, guided by the radiological and anatomical appearance at operation, the pH was always around or higher than 7.3 (cases 1 and 9). In case 27, although the obstructed kidney appeared radiologically functionless and was producing a urine with a pH of 7.6, it was preserved. However, 2 months after removal of obstruction there was no evidence of any radiological recovery.

The other function of the renal tubules that may be impaired in hydronephrosis is concentration of urine. Obstructed canine kidneys were found to produce urine with a lower osmolality and higher sodium concentration than the urine of the contralateral sound kidney (Berlyne and Macken, 1962; Jaenike and Bray, 1960). A similar finding was reported in obstructed human kidneys (Platts and Williams, 1963). In this series, however, our obstructed kidneys produced a urine with a lower specific gravity than the other side in only 73% in the absence of infection and in 77.7% in the presence of infection and a urine with a higher sodium concentration than the contralateral kidney in only 64% of cases in the absence of infection and in 33% of cases with infection.

The reason why the rest of the obstructed kidneys had urine with equal or higher specific gravity and lower sodium concentration than the urine of the contralateral sound kidney is unknown. It may be that the urine composition in those obstructed kidneys was modified by the effect of pyelovenous back-flow that is known to occur with hydronephrosis (Risholm and Obrink, 1958). This is probably why the specific gravity and sodium concentration of urine of hydronephrotic kidneys in this series did not correlate with severity of renal damage and degree of renal recovery and so both were judged to be of no help in prediction of recovery.

A kidney that may appear functionless on IV urography could possess a good recovery potential if obstruction has not affected its ability to acidify urine, a function which unfortunately cannot be explored radiologically. In this series there is evidence to suggest that the ability of renal tubules to acidify urine can stand obstruction longer than the ability of the tubules to concentrate urine (*e.g.* Case No. 18). This study also suggests that as long as an obstructed kidney is capable of acidifying its urine as demonstrated by a urinary pH lower than the pH of the blood, *i.e.* 7.3, there are good prospects for that kidney to recover after correction of the obstruction.

A surgeon dealing with lower ureteric obstruction resulting in a radiologically non-functioning kidney may rely on a quick estimation of urinary pH of the obstructed kidney at operation to determine whether or not the kidney in question is salvageable. This simple test is of great help, especially if the obstruction is low and the kidney is not accessible to look at through the same low incision. It is probably safe to admit that the test should be used to help surgeons to preserve badly obstructed radiologically functionless kidneys and hope for recovery whenever urinary pH is lower than 7.3. On the other hand, it would be dangerous to use the test for unnecessary removal of kidneys if other methods show some residual function, even when the pH reading of the urine is higher than 7.3.

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The Value of Provocative and Acute Urography in Patients with Intermittent Loin Pain

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Summary—Twenty-two patients with intermittent loin pain thought to be typical of primary pelvic hydronephrosis but with normal appearances at standard excretion urography were subjected to diuretic urography using Frusemide-induced diuresis.

If this was normal, acute urography was performed when the patient had pain. Abnormal appearances were shown in only 15 patients. In 4, only the erect films revealed the hydronephrosis. Dilatation occurred in response to a diuretic load in 9 and the abnormality was shown at the time of an attack of pain in 4. The hydronephrosis was shown only during the attack of pain in 2, a diuretic urogram having been normal. In 2 patients the nephrographic signs of acute obstruction were shown to be due to occlusion of the pelvi-ureteric junction at the time of an attack of pain. The importance of sequential examination, the value of erect films and acute urography are stressed.

A common problem in a urological patient is the diagnosis of intermittent loin pain where no abnormality is apparent on standard excretion urography. Some of these patients reveal a primary pelvic hydronephrosis on subsequent excretion urography. Wulff (1935) advocated urography within 48 h of a renal colic. Nesbit (1956) stressed the value of "acute" urography at the time of pain and Saxton (1969) confirmed these observations.

The value of a diuretic urogram as an additional tool in the demonstration of primary hydronephrosis was first stressed by Covington and Reeser (1950) using water as the diuretic agent. This was confirmed by Hanley in 1960. Since then, Mannitol (Johnson and Robinson, 1969), Frusemide (Saxton, 1969) and contrast medium (Nabor, 1975) have all been used to provoke the appearance of intermittent hydronephrosis. The value of prone films, erect films and infusion urography have all been stressed over the years.

We present a series of 22 patients who have had a combination of standard excretion urography, diuretic urogram, "acute" urography and erect films in order to diagnose the cause of loin pain.

Patients

Twenty-two patients were investigated from the urological clinics if they had intermittent loin pain. In some the pain was made worse by drinking; in others there was relief with the passage of large quantities of urine.

Methods

Each patient had an excretion urogram, diuretic urogram and some an "acute" urogram at the time of pain.

Diuretic Urography

Preparation by fluid restriction was as for standard urography. A plain film was taken and then 250 ml of 30% Urografin infused rapidly into an arm vein. A supine film was taken at 7 min after the start of the infusion and an erect film at 14 min. An injection of 20 mg of Frusemide was given intravenously and films taken at 5, 10 and 15 min after the injection. The examination was judged to be normal if washout was symmetrical and complete at 15 min and abnormal if there was increased distension or density on the affected side.

Acute Urography

After a plain film, 50 ml of Conray 420 was

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Table 1 Duration of Symptoms

	Normal urogram	*Hydronephrosis*
Symptoms present for:		
Less than 1 year	3	2
1 year	2	3
2 years	1	4
3 years	1	1
4 years		3
5 years		1
20 years		1
Total	7	15

injected, a nephrogram film taken at 1 min after the start of the injection, and a further film at 5 min. Subsequent films were carried out as judged necessary by the radiologist.

Table 2 Calyceal Anatomy

GROUP A		*GROUP B*	
Calyces dilated on standard urography	7	Calyces not dilated on standard urography	7
Dense nephrogram (acute urogram only)	1	Abnormal diuretic urography; hydronephrosis with dilated calyces	2
Erect film showed more dilatation	4	Abnormal diuretic urography; hydronephrosis with normal calyces	2
Diuresis showed more dilatation	2	Normal diuretic urography; hydronephrosis on acute urography	2
		Normal diuretic urography; no acute urography	1

One patient progressed from Group B to Group A and is excluded from the table.

Results

Twenty-two patients with recurrent attacks of loin pain were studied. The duration of symptoms varied from less than 12 months to nearly 20 years (Table 1).

Twelve patients presented with intermittent colicky pain, while in 10 it was constant and continuous during an attack. In some of them there were other features, *e.g.* 5 noted that the pain was precipitated by an increased fluid intake while another 5 had frequency of micturition at an attack. One patient presented with both these features while another patient had had a pyeloplasty and the symptoms were beginning to occur in the opposite side.

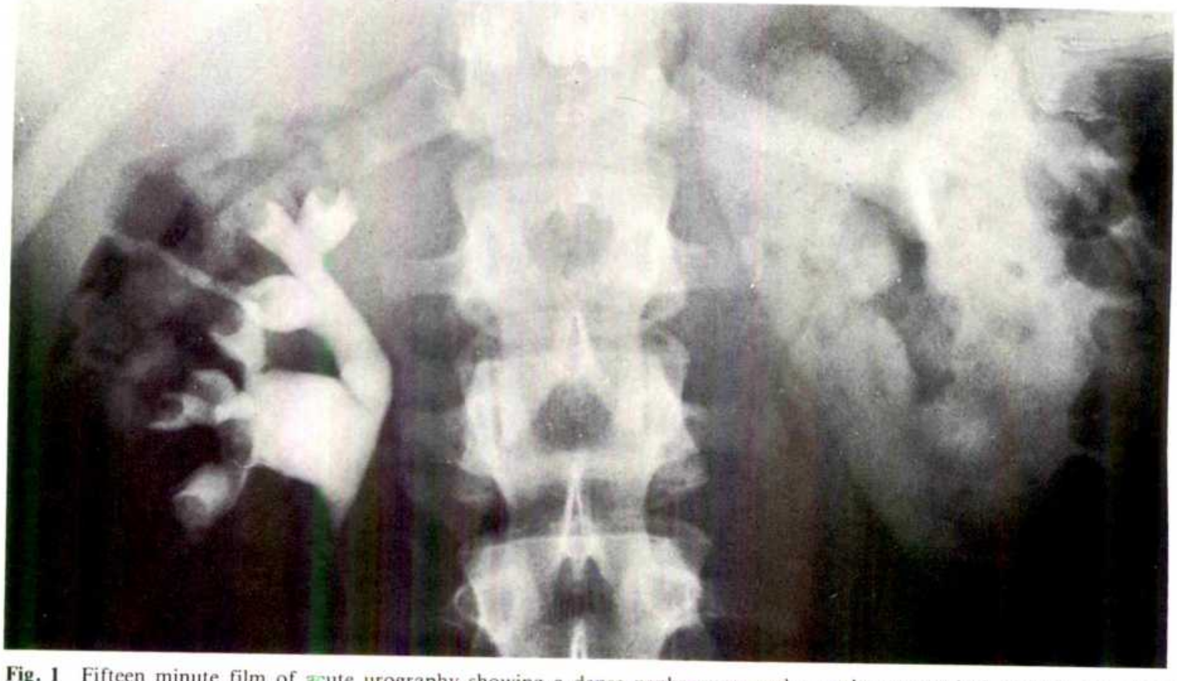


Fig. 1 Fifteen minute film of acute urography showing a dense nephrogram and a pyelogram typical of acute on chronic obstruction due in this case to pelvi-ureteric junction obstruction.

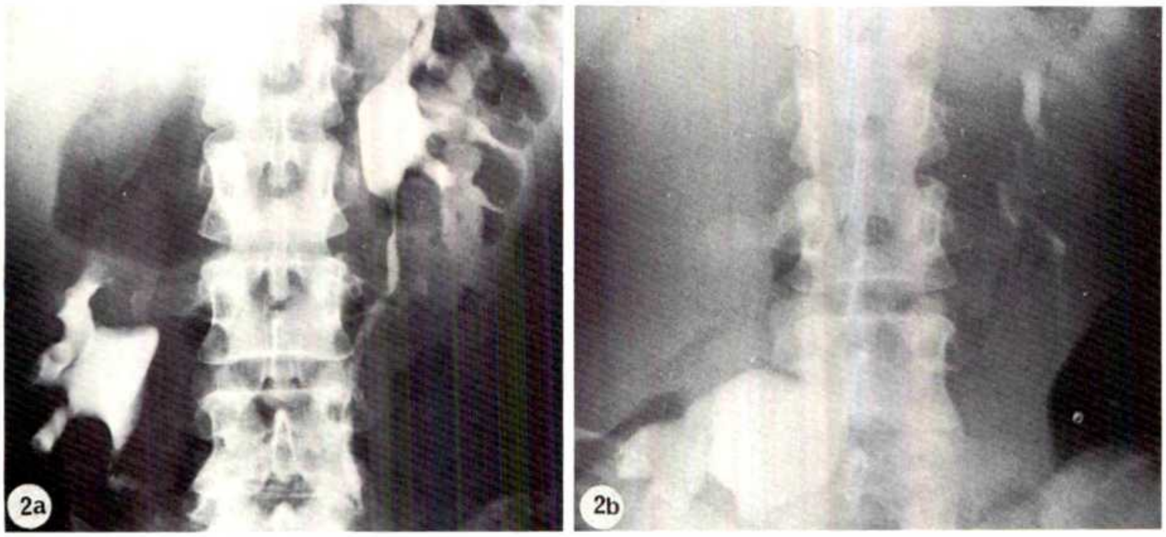


Fig. 2 (a) Supine film; minor calyces appear normal. (b) Erect film showing nephroptosis and hydronephrosis.

There were 17 females and 5 males. The pain was on the right side in 11 and on the left side in 12 while in 1 it was bilateral.

Our radiology demonstrated hydronephrosis in 15 patients only: 7 on the right side and 8 on the left.

Those that showed positive features fell into 2 groups (Table 2, A and B) depending on whether they had calyceal dilatation at standard excretion urography. Group A consisted of 7 patients who had calyceal dilatation at standard excretion urography. In 3 this was minor, but in 4 changes were obvious. In the latter group, as the renal pelvis dilated it was noted that the kidney rotated on its long axis. In addition, there were other special features. One patient with a long-standing history of pain was examined during an acute attack of pain and showed features of acute on chronic obstruction (Fig. 1). In 4 it was only the erect film that showed calyceal clubbing (Fig. 2b), and when films were taken supine, even with diuresis the features were much less marked (Fig. 2a). Of the 7 patients in Group B diuretic urography elicited abnormalities not detected at standard excretion urography in 4. Two of these patients demonstrated the features of classical primary pelvic hydronephrosis (Figs. 3a and b) and the other 2 showed only pelvic dilatation without blunting of the fornices (Figs. 4a and b). In 1 of these 2 patients, forniceal changes did

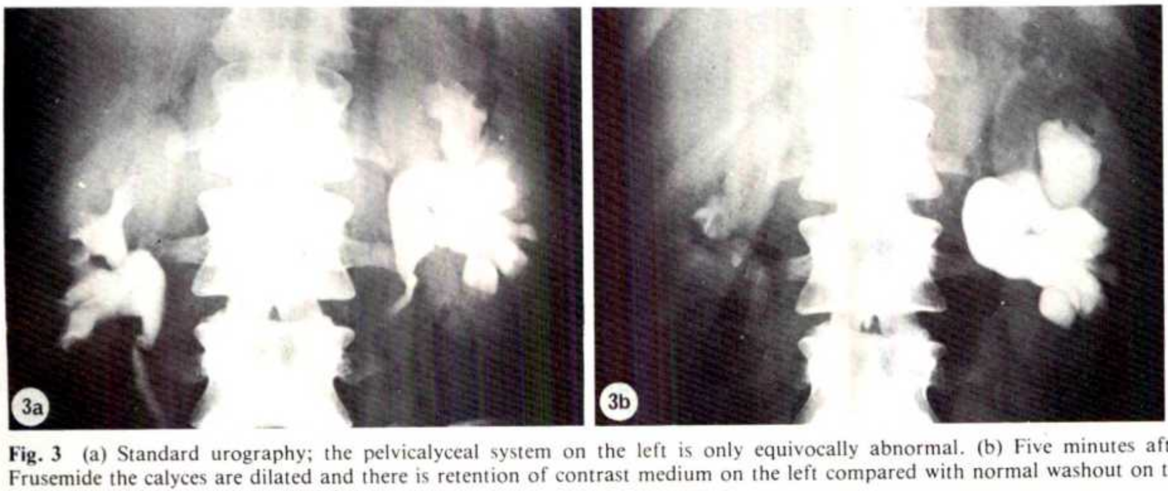


Fig. 3 (a) Standard urography; the pelvicalyceal system on the left is only equivocally abnormal. (b) Five minutes after Frusemide the calyces are dilated and there is retention of contrast medium on the left compared with normal washout on the right; the pelvis is now of the closed type.

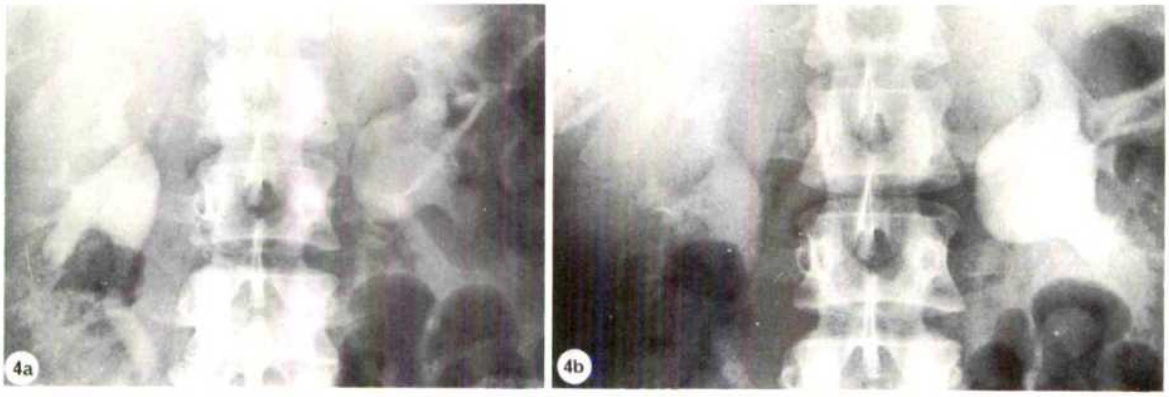


Fig. 4 (a) Before diuretic but after a large dose of contrast medium the pelvis has an ampullary appearance but the pelvi-ureteric junction is at the most dependent part. Note the serpentine appearance of the upper ureter and the decreased density of the left pelvis with respect to the right. (b) After diuresis the junction is now occluded and there is retention of contrast medium with increased density of the left compared with the right side. The calyces remain normal.

not occur even when urography was performed during an acute attack of pain.

The 3 patients with normal diuretic urograms fell into 2 groups. In 2 the hydronephrosis was demonstrated during an acute attack of pain (Figs. 5a, b and c). The third patient did not have an acute urogram and was operated upon in spite of negative radiological features and the hydronephrosis demonstrated with a water load at that time.

Two patients, 1 with a normal urogram and the other abnormal (Fig. 1), when examined acutely showed an increasingly dense nephrogram such as is seen in acute ureteric obstruction due to stone but without an obstructive agent other than the occluded pelvi-ureteric junction.

There were 4 patients with hydronephrosis in whom the diuresis did not reproduce their pain. However, 2 without hydronephrosis had pain on diuresis.

Twelve patients had pyeloplasties, 3 a nephropexy, while 1 had both operations. There was total relief of symptoms in all those who had positive urographic features.

Discussion

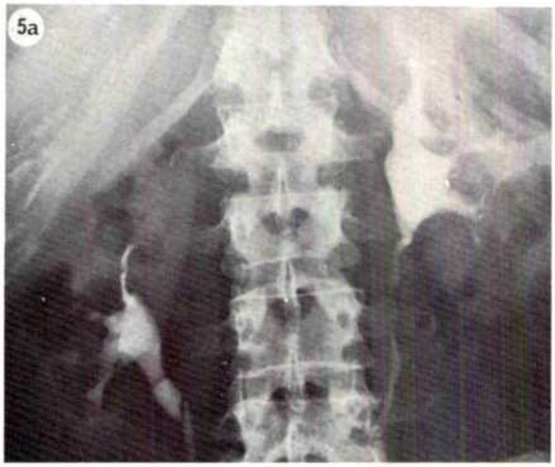
The main aim of renal surgery is to preserve renal function. The object of our sequential investigation was to identify patients before irreversible changes had occurred in the renal parenchyma or pelvis (Brenez, 1969). Although the patients had had symptoms for periods of up to several years standard urography was normal but our sequential investigation demonstrated the cause of the pain and all patients were relieved by surgery.

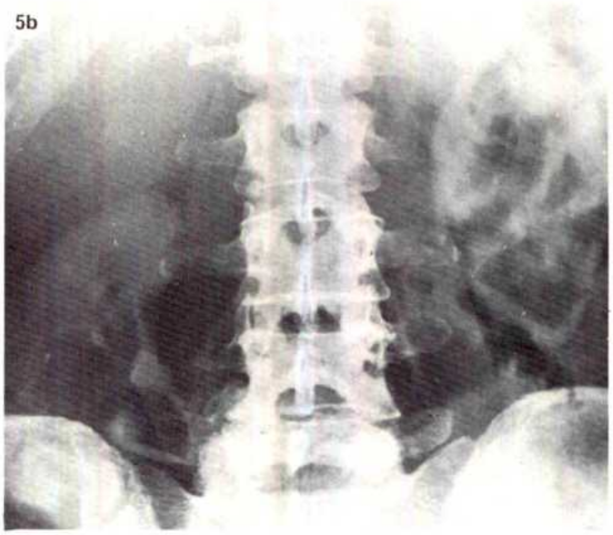
The value of the erect film in the investigation of the "baggy pelvis" has been recognised for many years (Saxton, 1969); it may show free drainage or accentuate the obstruction. In the 4 patients who had hydronephrosis on the erect film, the diuretic urogram showed free drainage in the supine position; thus this condition could be identified only by taking an erect film. All 4 patients were successfully treated by nephropexy and pyeloplasty at the same operation.

Blunting of the calyceal fornices has been taken as the hallmark of hydronephrosis (Gibson, 1956) but we found that some of our patients had pain from pelvic dilatation during both acute and diuretic urography. Their symptoms were relieved by pyeloplasty. Thus we believe that the minor calyces need not be clubbed on the urogram to diagnose surgically correctable hydronephrosis (Table 2).

Two patients had normal standard and diuretic urography but showed a hydronephrosis during an attack of pain. The circumstances that caused these acute episodes were not clear but they indicate the importance of examination during an attack of pain (Nesbit, 1956). Our working rule has been that a normal urography during an attack of pain means that the pain is not due to an anatomical renal abnormality.

Two of our patients had dense nephrograms at the time of an acute attack; a dense nephrogram occurs with a high pressure in the renal pelvis due to ureteric obstruction (Johnston, 1969; Bretland, 1972) and is presumptive evidence of a





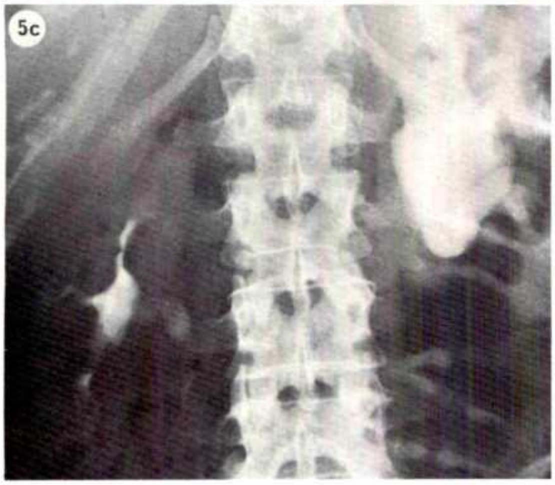


Fig. 5a Urography before diuretic showing a normal pelvicalyceal system.

Fig. 5b After diuretic there has been normal washout of contrast medium without any dilatation of the collecting system.

Fig. 5c Acute examination showing a primary pelvic hydronephrosis; the calyces are normal.

high grade obstruction at the pelvi-ureteric junction.

Our method of diuretic urography converts the kidney from a water-retaining state to a water-losing state in a few minutes; in abnormal kidneys this is accompanied by a change in the anatomy (Fig. 4). It is easy and not more lengthy than standard excretion urography and has a satisfactory diagnostic yield, 9 of our 15 cases being proved abnormal by diuretic urography.

We conclude that diuretic urography with erect films, followed by acute urography if diuretic urography is normal, is a necessary sequence of investigations in patients with undiagnosed intermittent loin pain.

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Ureteric Reimplantation for Vesico-Ureteric Reflux in the Adult

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Summary—A retrospective study of 32 adult patients undergoing ureteric reimplantation for reflux has been carried out.

Reflux and reimplantation in relation to urolithiasis, pregnancy, renal failure, hypertension and bladder neck obstruction have been discussed. Eighty-four per cent of patients with primary reflux had pyelonephritic scarring compared with only 34% of patients where reflux was secondary.

Reimplantation has been technically successful in preventing reflux in every patient in this series, with 18 patients (65%) becoming symptom free. Pyelonephritis, hypertension and renal failure were not significantly improved but no progressive changes were observed in the follow-up period after reimplantation.

Vesico-ureteric reflux in adults has rarely received the clinical attention that it deserves. Its association with chronic pyelonephritis and, to a lesser extent, hypertension is well recognised but little is known of its aetiology or pathogenesis. In its mildest forms reflux may be either asymptomatic or, when symptomatic, may be easily managed conservatively.

The reported incidence of vesico-ureteric reflux in adults is variable. Estes and Brooks (1970), after studying 903 cystourethrographies in adults with chronic urinary infections, obstructive uropathy, neurogenic bladder incontinence and urinary trauma, found 5% to have reflux, but other authors quote incidences varying from 4 to 25% (Valadka *et al.*, 1960; Dodge, 1963; Ross, 1965). It is likely that the apparent increase in the diagnosis of reflux may be due to the more frequent use of micturating cystourethrography (Lipsky and Chisholm, 1971) in the investigations of the adult urinary tract.

Material and Methods

During the 11 year period from 1965 to 1976 a study was made of all patients at the United Bristol Hospitals undergoing ureteric reimplantation for vesico-ureteric reflux. This study revealed a total of 32 patients with vesico-ureteric reflux who had ureteric reimplantation following failure of conservative management. This represents 49% of all the ureteric reimplantation in adults carried out in the 11 year period. The youngest patient in this series was 17 years and the eldest 57 years (mean age 33 years). An excretion urogram and a micturating cystourethrogram were carried out on all patients. The severity of reflux was recorded using the following scale: Grade I—minimal reflux into the lower ureter. Grade II—reflux to the kidney without dilatation of either ureter or pelvis. Grade III—reflux to the kidney with ureteric and pelvic dilatation. Using these criteria, the severity of reflux in this group is as shown in Table 1.

The various causes of reflux are shown in Table 2, the commonest cause being primary vesico-ureteric reflux. Three patients in the iatrogenic group developed reflux after incision of ureterocoele. In 5 patients a degree of bladder

Table 1 Grading of Vesico-Ureteric Reflux

Grade I	0
Grade II	5
Grade III	27
Total	32

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Table 2 Aetiology of Vesico-Ureteric Reflux

Primary	15 (47%)
Secondary	
Iatrogenic	5 (15.6%)
Bladder neck obstruction	5 (15.6%)
Calculi	3 (9.3%)
Double ureter	3 (9.3%)
Neurogenic bladder	1 (3%)
Total	32

outlet obstruction was considered to be the cause of reflux. Two of the 3 patients with lithiasis developed reflux after diagnosis of stone and in the third patient the reflux and stone were diagnosed at the same time. The 1 patient with a neurogenic bladder developed reflux 12 months after excision of a caudal tumour.

The presenting symptoms were variable (Table 3). Loin pain was invariably associated with urinary infection. When infection was present the causative organism was a coliform in every patient with the exception of 1 who had a *Proteus*. Pyrexia was rarely seen and in no case did a pyonephrosis develop. In 7 patients there was a mild degree of renal failure and 1 patient had severe uraemia. Hypertension was noticed in 4 patients.

Excretion urography demonstrated pyelonephritic changes varying from slight distortion of the calices to multiple scars in 26 patients. In 19 patients urography demonstrated varying degrees of upper tract dilatation.

Cystoscopy was carried out on all patients and usually showed the presence of a patulous ureteric orifice.

Twenty-six patients had ureteric reimplantation alone; 3 had reimplantation and a V-Y plasty of the bladder neck and of these 2 had the reimplantation carried out at the same time whilst in the third patient a V-Y plasty was carried out several years before reimplantation. In 1 patient ureteric reimplantation was carried out at the same time as a bladder neck incision and a diverticulectomy; in another patient a transurethral resection of bladder neck as well as reimplantation was carried out and finally 1 other patient had the reimplantation combined with a ureteric tailoring.

Double ureters were reimplanted separately but using the same submucosal tunnel. In all cases the technique of ureteric reimplantation used was as described by Politano and Leadbetter (1958).

Table 3 Presenting Symptoms

Urinary tract infection	23 (72%)
Loin pain	23 (72%)
Dysuria	18 (56%)
Renal colic	8 (25%)
Renal failure	7 (22%)
Hypertension	4 (13%)
Pyrexia	3 (9%)
Enuresis	3 (9%)
Residual urine	2 (6%)
Urinary incontinence	1 (3%)

Results

Post-operative information was not sufficiently detailed in 2 patients who had ureteric reimplantation for primary reflux and 2 patients who had reimplantation for secondary reflux; all 4 were therefore excluded, leaving 28 patients for post-operative review. The follow-up period ranged from 1 to 11 years (mean 4.5 years). In no patient was persistent or recurrent reflux detected. Eighteen patients (65%) were symptom free, whilst 10 (35%) had persistent symptoms (Table 4).

Hypertension persisted in the 4 patients after ureteric reimplantation but 1 patient did become normotensive after a later nephrectomy. One patient with mild renal failure improved following reimplantation and the other 6 remained unchanged but no worse.

One patient developed ureteric stenosis and a secondary stone in the lower ureter; a ureterolithotomy and a repeat reimplantation were performed with success. One patient with severe hydronephrosis showed no improvement following ureteric reimplantation and a subsequent nephrectomy was performed. Recurrent infection was seen post-operatively in 9 patients, 8 of whom presented with loin pain.

Three female patients became pregnant 1 or

Table 4 Post-Operative Symptoms

Urinary tract infection	9 (28%)
Loin pain	8 (25%)
Dysuria	8 (25%)
Renal failure	6 (19%)
Hypertension	4 (13%)
Renal colic	2 (6%)
Enuresis	1 (3%)
Pyrexia	1 (3%)
Residual urine	1 (3%)
(Mean follow-up 4.5 years)	

more times after ureteric reimplantation. One of these patients had a moderate degree of renal failure which did not worsen during the pregnancy; another had hypertension which remained unchanged. The third patient had a hydronephrosis which became marginally worse during pregnancy. It was thought that this was due to her pregnancy rather than recurrent reflux. Postnatal micturating cystourethrography confirmed the absence of any reflux in each of these 3 patients.

Discussion

The occurrence of vesico-ureteric reflux in infancy and childhood is well recognised. The natural history in children would seem to be that reflux will often disappear spontaneously as the child grows and the infection is controlled. Baker *et al.* (1966) suggested that there was a spontaneous cure rate of 80%. The disappearance of reflux is generally believed to be due to lengthening of the intravesical ureter and/or the development of the musculature of the uretero-vesical junction (Hutch, 1961; Stephens and Lenaghan, 1962). Primary reflux in the adult has been recorded in several studies but no precise figures for the incidence are available (Hodson and Edwards, 1960; Zingg, 1967; Ambrose, 1969; McGovern and Marshall, 1969). Lipsky and Chisholm (1971) suggested that the incidence may be higher than that recorded in the literature.

Fifteen (47%) of the patients in this series undergoing ureteric reimplantation had primary vesico-ureteric reflux. Nine were under 30 years of age. Pyelonephritic scarring was seen on excretion urography in 13 (87%). The length of history was significantly longer in patients with primary reflux than those whose reflux was secondary. The majority of these patients had recurrent urinary infections dating back to childhood, which would seem to support the view of the importance of infection on the continuation of childhood reflux or on the recurrence of reflux (Estes and Brooks, 1970).

Five (16%) of the patients in this series developed vesico-ureteric reflux following instrumentation to the ureteric orifice. This compares with the 23% reported by Estes and Brooks (1970).

Three patients with vesico-ureteric reflux were found to have upper urinary tract calculi and in all of them there was infected urine. Amar *et al.* (1968) suggest that the presence of urinary calculi, urinary tract infection, structural changes at the vesico-ureteric junction and reflux may together interact in such cases. Long-standing stone causes chronic infection and this leads in turn to changes at the vesico-ureteric junction. Reflux is known to perpetuate urinary tract infection and this may contribute to the formation of urinary tract calculi. Amar *et al.* (1968) stressed that infected upper urinary tract calculi, especially the staghorn variety, should always be investigated to exclude vesico-ureteric reflux. This series would give modified support to this concept. Vesico-ureteric reflux in the presence of ureteric duplication is well recognised (Ambrose and Nicholson, 1964; Amar and Hutch, 1968). In the case of complete duplication the reflux occurs most frequently into the upper or orthotopic ureter because of its less oblique and shorter intramural course.

Reflux secondary to neuropathic bladder disease is well known (Bunts, 1958; Damanski, 1965). One patient in this series had a neuropathic bladder with reflux. Follow-up 8 years after reimplantation revealed no evidence of recurrent reflux.

Hypertension in this series has not been influenced by successful vesico-ureteric reimplantation. Nephrectomy, in 1 patient with hypertension, was successful in returning the blood pressure to a normal value.

The findings on urography revealed a significant difference between those patients who underwent reimplantation for primary reflux compared to those where this operation was performed for secondary reflux. Eighty-four per cent of patients who had primary reflux had gross pyelonephritic changes, whereas only 35% of patients with secondary reflux had such changes.

Renal failure was not a contra-indication to reimplantation of the ureter. In only 1 patient did the degree of renal failure improve; however, in no patient did it get worse. It would seem that successful reimplantation may prevent progressive renal failure.

Conclusion

Vesico-ureteric reflux in adults is a definite clinical entity. In the majority of patients this is a primary reflux. However, it is important to realise that there is another group where there is secondary reflux. Such secondary reflux may be associated with a wide variety of conditions such as bladder neck obstruction, following surgery to the ureteric orifice, duplication, calculi and the neuropathic bladder. The presence of these conditions should always suggest the possibility of secondary reflux. Likewise, the possibility of primary reflux should be suspected in those patients in whom there is renal scarring or recurrent urinary sepsis in the absence of obstruction.

Vesico-ureteric reflux in its mildest forms can be asymptomatic or, when symptomatic, may be managed conservatively. However, when reflux is severe or when conservative management has failed, then vesico-ureteric reimplantation should be considered.

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The Site of Recurrence of Non-Infiltrating Bladder Tumours

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Summary—A study of 56 cases of non-infiltrating bladder tumour showed a striking difference in the distribution within the bladder of the primary and the recurrent tumours. More than three-quarters of the primary tumours were confined to a restricted area near a ureteric orifice whereas only one-fifth of recurrent tumours were found in this site. By far the commonest site for recurrent tumours was the postero-superior wall of the bladder. Forty-five recurrent tumours formed in the air bubble region, a site in which no primary tumour was found in the whole series.

The postero-superior wall of the bladder is subject to mild trauma and abrasion by the tip of an endoscope and the air bubble region is the recipient of hot gas produced by the diathermy. These gas bubbles may also convey detached tumour cells to the recipient site.

Local trauma may encourage tumour formation either by producing a raw surface which allows implantation of tumour cells, or possibly also by reducing local resistance to the primary carcinogenic factor.

Non-infiltrating bladder tumours frequently recur after treatment. If recurrence is to be prevented it is necessary to know exactly by what process the fresh tumours are generated. A recurrence may be caused by the continued action of the carcinogenic factor that caused the primary tumour. If this were the case virtually nothing could be done to prevent recurrences because our present knowledge of aetiology has not reached the stage of providing an effective weapon. On the other hand it has long been suspected (McDonald and Thorson, 1956) that a recurrence may be due to the implantation of cells brought about by the endoscopic treatment of the original tumour. Several measures could be taken to prevent recurrence if implantation was known to be the cause.

We have reported a study of non-infiltrating bladder tumours treated by endoscopic diathermy resection and followed up by periodic cystoscopy for at least 2 years. This series comprised 2 groups of cases, one of which was given a small dose of irradiation (Cobalt 60) within a few days of the primary treatment in the hope of preventing recurrence. A control group was treated identically except that it did not receive irradiation (Page *et al.*, 1978). When this trial began it was accepted that implantation was one of the possible factors in recurrent tumour formation although the evidence was speculative. As the study progressed, it became evident that the sites of the tumours, primary and secondary, fell into certain patterns and that there was a striking difference between the site of the primary tumour on the one hand and of the recurrences on the other. A consideration of the sites of the recurrent tumours suggested that they had a different aetiology from the primary tumour and that the distribution of the recurrent tumours was positively in favour of the implantation hypothesis.

Materials and Method

The series comprised 56 cases of which 29 received irradiation. None of the cases had received previous treatment. They were all treated initially by endoscopic diathermy resection and the diagnosis of non-infiltrating transitional-cell tumour was established by histology. Each case was followed up by periodic cystoscopy for at least 2 years. The first follow-up cystoscopy was done about 3 months after primary treatment and thereafter the interval between cystoscopies was steadily extended if there was no recurrence of tumour but it was never longer than one year.

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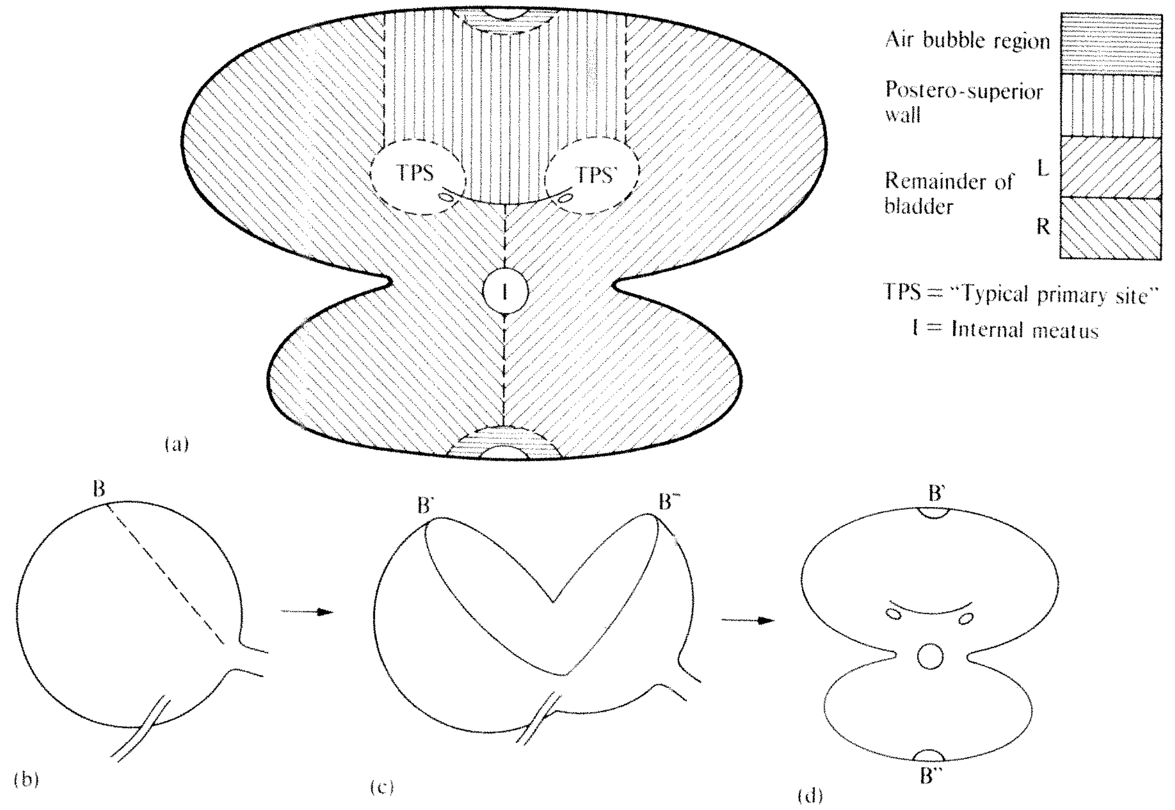

Fig. 1 (a) Plan of internal surface of bladder with sites demarcated. (b), (c) and (d) explain the basis of the plan shown in (a). (b) shows the line of the imaginary incision running across the bladder through the site of the air bubble. (c) shows the bladder opened up and (d) shows the resulting plan. The 2 halves of the air bubble are at B' and B''.

Table 1 Comparison of Sites of Primary and Recurrent Tumours

	Primary		*Recurrent*		*Radiated and control group combined*	
	Irradiated	*Control*	*Irradiated*	*Control*	*Primary*	*Recurrent*
Typical primary site only	23	20	2	3	43	5
Elsewhere only	2	1	0	4	3	4
Both sites	4	6	15	9	10	16
Totals	29	27	17	16	56	25

In the resection of the primary tumour glycine was always used as irrigant. Recurrent tumours, if they were small and few, were treated by fulguration in out-patients and water was used as irrigant. Glycine was used for any recurrences deemed to require in-patient treatment whether they were treated by resection or fulguration or by both.

In the follow-up 3 patients had additional forms of treatment. Two received one course of intravesical thiotepa each. The third patient received 2 courses of epodyl and as these proved ineffective cystectomy was done.

Findings

In order to chart the sites a scheme was devised and is shown in Figure 1. Table 1 gives the distribution of the tumours in a simplified form. With the primary tumour it was remarkable how

Table 2 Number of Recurrent Tumours According to Site

Site		*Irradiated group 17 cases*	*Control group 16 cases*	*Total tumours in each site*
A	Typical primary: ipsilateral	85	56	141
B	Typical primary: contralateral	5	29	34
C	Postero-superior wall	97	141	238
D	Air bubble region	17	28	45
E	Remainder of bladder: ipsilateral	62	34	96
F	Remainder of bladder: contralateral	7	17	24
Totals		273	305	578

constant the site was. This predilection for one particular site is unexplained and its significance is not known. In a high proportion of cases the primary tumour was in a fairly small area of the bladder running upwards and outwards from one of the ureteric orifices. This area may be called the "typical primary site". As Table 1 shows, there was only one case in which this site was not involved, and in 43 of the 56 cases the primary tumours were confined to this site (*i.e.* there were no tumours elsewhere). The site is an area of perhaps 5 cm diameter and represents a small fraction of the total internal surface of the bladder.

The site of recurrent tumours on the other hand was much less constant and restricted. Although recurrences were often found in the "typical primary site" they were also frequently found in other sites, quite unlike primary tumours. The postero-superior wall of the bladder was a very common site for recurrent tumours, but relatively uncommon for primaries. The importance of the postero-superior wall became even more striking if account was taken of the total number of tumours forming on it throughout the course of the cases (Table 2). It accounted for many more tumours than any other site. It should, however, be pointed out that the incidence was very uneven comparing case with case, and 178 of the total of 238 tumours were accounted for by 8 of the 21 cases having recurrences in this site. Another striking site for recurrent tumours is the small area of the bladder where the air bubble settles. It is an extremely rare place for a primary tumour (not one was found in this site in the present series) but it is a common site for recurrences.

The following case illustrates the contrast between primary and recurrent tumours.

Mr A. C., aged 70, was referred with a month's history of haematuria. In January 1969 cystoscopy showed (Fig. 2) a solitary papillary tumour in the region of the left ureteric orifice. It was treated by endoscopic diathermy resection. Six months later cystoscopy revealed no tumour but in October 1969, 9 months after the resection of the primary tumour, cystoscopy showed numerous tumours scattered over the postero-superior wall of the bladder and in the air bubble region. They were treated by cystodiathermy but continued to recur, mostly in the same parts of the bladder, and further cystodiathermy was done on 2 further occasions. In July 1971 a course of thiotepa was given. After this there was one further recurrence (a solitary tumour on the postero-superior wall) in February 1972. At his last cystoscopy, in May 1972, the bladder was clear. He now had a carcinoma of the bronchus with secondaries and was not seen again. He had been in the control group of the trial and so had not had irradiation of his bladder.

Discussion

The differences between the patterns of primary and recurrent tumours suggest that their aetiology may be different or at least that there is an additional factor causing recurrences, and that this factor may be introduced at the time of the treatment of the primary. There are 2 ways in which the primary treatment might bring about fresh tumour formation. One is by "seeding" of detached tumour cells. McDonald and Thorson (1956) have shown that tumour cells inserted into an isolated pouch of the bladder in the dog can lead to the formation of tumours. It is likely that in the intact bladder conditions would be far less favourable, but the possibility of seeding or implantation may be accepted. Indeed Weldon and Soloway (1975) have recently shown that tumours can be produced by instilling into the

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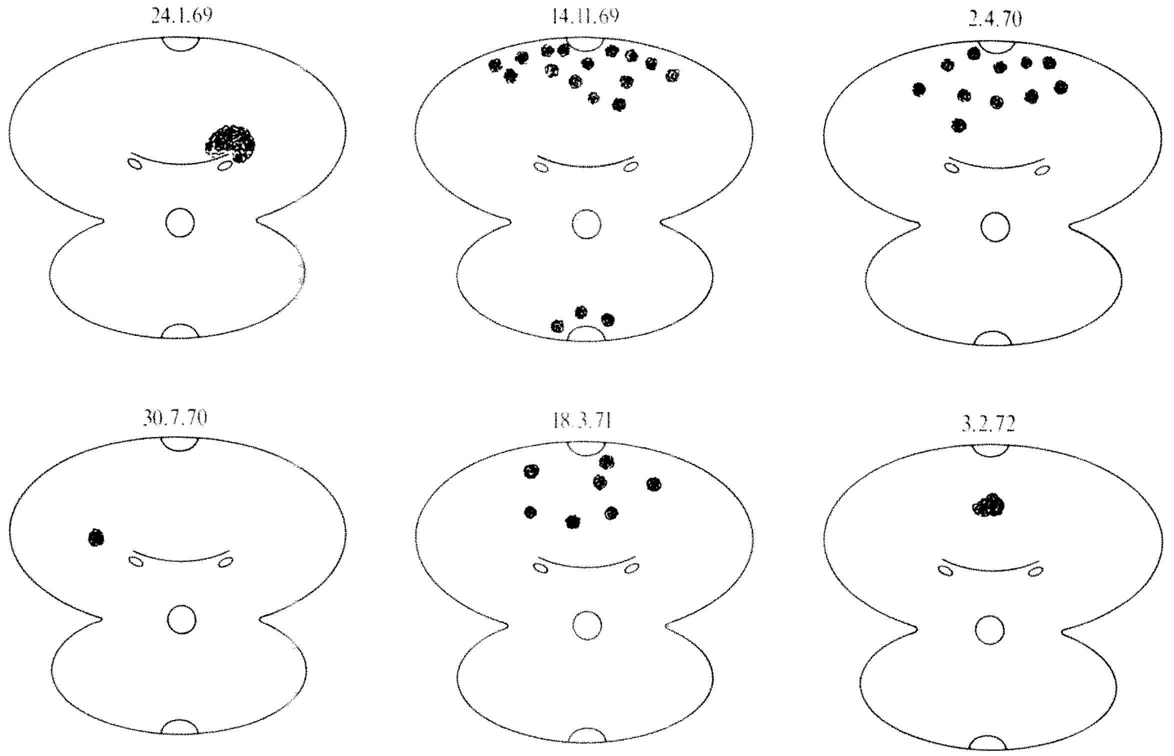

Fig. 2 Bladder plans showing sites of tumours at all positive cystoscopies in the illustrative case.

bladders of normal mice a suspension of tumour cells from other syngeneic mice in which bladder tumours had been produced by feeding them with a carcinogen. The second way arises out of the trauma to the vesical mucosa caused during the endoscopic treatment of the original tumour. Trauma might act in 2 ways. Firstly, it might facilitate the reception of "seeds" by causing a breach of the mucosal surface. Secondly, by lowering the resistance of the tissues it might determine the site at which the original carcinogenic factor would induce tumours to form. Here again Weldon and Soloway's experiments are relevant. Whereas only 13% of mice with previously normal bladders developed tumours after instillation of tumour-cell suspensions, 60% developed tumours if a chemical cystitis had been produced 48 h before the tumour cells were instilled.

Trauma of 2 different kinds could explain the 2 characteristic patterns of recurrent tumour distribution previously mentioned. The posterosuperior wall of the bladder, such a common site for recurrent tumours, is exactly that part of the bladder that is always scraped and prodded by the end of the cystoscope or resectoscope when it lies in its neutral position, particularly when the bladder is relatively empty (for example, when the instrument is introduced).

The part of the bladder in which the air bubble lies might be subject to a different form of trauma, namely heat. The gas generated by the action of diathermy on tissues is of course extremely hot and this gas rises immediately to the region of the air bubble. Although it must cool a little as it floats upward through the medium it is reasonable to assume that it is still hot enough on reaching the ceiling mucosa to cause some thermal trauma. Indeed, one does get the impression during a fairly long cystodiathermy that the mucosa in the air bubble region becomes hyperaemic. It should be emphasised that the kind of trauma (whether it is mechanical or thermal) that may weaken the resistance of tissues to the action of a carcinogen must not be severe enough actually to kill the tissues. Lethal trauma is always produced at the actual site of diathermy resection or fulguration, and these are sites at which fresh tumours do not commonly occur when the primary tumours are non-infiltrating.

The air bubble site is also exposed to the risk that the bubbles of diathermy gas contain tiny fragments of viable tumour and deposit them on the mucosa.

Reference to Table 2 shows that recurrent tumours were more numerous on the same side as the primary tumour than in any other site except the postero-superior wall. This may be explained in 2 ways. Firstly, it would be subject to incidental mechanical and thermal trauma during the diathermy of the primary tumour, much more than its contralateral partner. Secondly, it could well be that this area of the bladder is still subject to the original factor that produced the primary tumour here. Perhaps these fresh tumours are new primary tumours and have nothing to do with previous treatment.

The recurrent tumours rarely occurred in the scar of the previous diathermy. However, identification of the primary site is somewhat arbitrary and it is often difficult to decide if a tumour should be allocated to one site or an adjacent site on the bladder map. Recording cystoscopic findings on a chart is inevitably an approximation.

The contralateral "typical primary site" (Fig. 1) had fewer tumours than its ipsilateral partner (34 against 141), demonstrating the tendency of recurrent tumours to predominate on the same side as the primary tumour, but even so this relatively small area of the bladder produced more tumours than the rest of the contralateral bladder, which constitutes a much larger area than the primary site. This again suggests that the primary sites are basically more susceptible to tumour formation.

We have shown that irradiation did not affect the total number of recurrent tumours (Page *et al*, 1978). The question arises, "Did irradiation influence the *distribution* of recurrences among the various sites?". Although it may appear from Table 2 that there appears to be a considerable difference between the 2 distributions, in fact this is largely accounted for by 1 or 2 patients with many recurrences (*e.g.* a patient in the control group with 50 on the postero-superior wall) and it is doubtful whether any conclusions as to the effect of irradiation on the site-pattern of recurrences would be justified. There is only one site (site B, the air bubble region) where there is any evidence of the distribution's being affected by irradiation; there was 1.0 recurrence at this site per patient in the irradiated group compared with 1.8 per patient in the controls. This difference does not approach statistical significance and it would need a much larger series to confirm this finding.

Table 3 demonstrates how the number of recurrences per patient varies from site to site. All but 5 of the 33 patients had at least one recurrence at site A but in terms of number of recurrences the most "popular" site was site C with an average of 7.2 recurrences per patient. This high figure was largely accounted for by 3 patients with respectively 31, 34 and 50 recurrences at this site; there were 12 patients with no recurrence here.

It is concluded that the distribution of recurrent tumours within the bladder is consistent with their being caused by implantation of tumour cells

Table 3 Distribution of Number of Recurrences per Patient at Various Sites. Irradiated and Control Groups Combined

Site	*Mean number of recurrences per patient**	*Number of patients with following number of recurrences at each site*							
		0	*1*	*2-5*	*6-10*	*11-20*	*21-30*	*31-40*	*41-50*
A Typical primary ipsilateral	4.3	5	6	10	10	2	–	–	–
B Typical primary contralateral	1.0	24	5	3	–	–	1	–	–
C Postero-superior wall	7.2	12	5	7	1	3	2	2	1
D Air bubble region	1.4	18	8	3	4	–	–	–	–
E Elsewhere ipsilateral	2.9	20	6	1	3	2	1	–	–
F Elsewhere contralateral	0.7	23	5	4	1	–	–	–	–

* The mean is based on all patients having a recurrence anywhere.

scattered by the primary treatment. The site of implantation is probably determined by mild mechanical trauma (including abrasion) of the recipient mucosa caused by the endoscopic instrument. Recurrences in the air bubble region may be determined by 2 factors: tumour cells are probably carried up to this site by bubbles of gas and the mucosa may suffer thermal trauma from this hot gas. It is possible that the growth of fresh tumours in traumatised sites is due to the lowering of their resistance to the primary carcinogenic factor.

Addendum

After the study here described had been completed Boyd and Burnand (1974) published a report drawing attention to the distribution of recurrent tumours with particular reference to the "vault of the bladder".

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Results of Prolonged Bladder Distension as Treatment for Detrusor Instability

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Summary—Forty-six patients with urinary symptoms associated with unstable (uninhibitable) detrusor contractions have been treated by a total of 58 bladder distensions; 43 of these were fully re-evaluated urodynamically thereafter and none showed conversion from unstable to stable detrusor behaviour. Four patients with unstable bladders were symptomatically improved but 5 patients reported symptomatic deterioration. We have concluded that while over-distension may sometimes improve a patient's symptoms, it did not result in the abolition of detrusor contractions or the reversal of unstable detrusor behaviour.

Normal people are able to inhibit detrusor contractions until it is physically and socially convenient for them to pass water. Patients with unstable bladders lack this ability. The abnormal uninhibitable detrusor contractions may occur in response to a variety of commonplace stimuli such as bladder filling, coughing and standing up. They often give rise to inconvenient and embarrassing symptoms such as frequency, nocturia, urgency and even urge incontinence and enuresis (Bates, 1971).

Treatment of detrusor instability is unsatisfactory. If instability is associated with outflow obstruction in males then relief of the obstruction often results in a return to stable bladder function. When it is present in unobstructed males and in females the problem is much more difficult. Medical treatment with a variety of drugs including propanthelene, imipramine, emepromium bromide, flavoxate, and bromocriptine have been disappointing. Surgical measures such as cystolysis or pre-sacral neurectomy (Worth and Turner-Warwick, 1973) or selective sacral neurectomy (Torrens and Griffiths, 1974) have also had unpredictable results in detrusor orientated abnormalities.

Recently the prolonged bladder distension technique developed by Helmstein (1972) has been a suggested treatment of bladder instability with encouraging results in those patients who had had symptoms all their lives and whose instability was presumably congenital (Dunn *et al.*, 1974; Ramsden *et al.*, 1976). The aim of the present study, begun in 1974, was to assess the effects of distension on instability of acquired as well as congenital origin.

Patients

We have performed 58 distensions on 46 patients (33 females, 13 males) aged between 11 and 71 years (mean 38 years). Ten of these patients have had a second distension and 2 have had a third. All were referred to the Urology Department at the Middlesex Hospital with symptoms suggestive of detrusor instability—urgency, urge incontinence, nocturia or enuresis. A careful history was taken, a full examination carried out and routine investigation such as urine analysis and intravenous pyelography performed. The clinical suspicion of detrusor instability was confirmed urodynamically by the method of synchronous pressure-flow videocystography developed by Bates *et al.* (1970) and detailed by Bates and Corney (1971). As a result of these investigations each patient's detrusor instability was allotted to 1 of 4 groups:

1. *"Congenital"*—13 patients—patients in this group had symptoms since childhood.
2. *Late Onset Idiopathic*—23 patients—this is by far the largest group. No cause or significant associated disease could be found.
3. *Neuropathic*—9 patients—patients in this group had signs of neurological disease confirmed by a consultant neurologist who diagnosed multiple sclerosis in all 9 cases.

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4. *Post-obstructive*—1 patient. Detrusor instability associated with male outflow obstruction usually, but not always, resolves following relief of the obstruction (Turner-Warwick *et al.*, 1973). Those cases that do not resolve may represent those patients with idiopathic instability which happened to have occurred at the same time as their outflow obstruction. However, this is not at all certain, so that the 1 post-obstructive patient in this series has been placed in a group of his own rather than in the idiopathic group.

Hypersensitive bladder states such as interstitial cystitis or trigonitis do not feature in this review because they are rarely associated with detrusor instability (Worth and Turner-Warwick, 1973).

Methods

After full explanation the patients were admitted to hospital and bladder distension performed by a technique similar to that described by Dunn *et al.* (1974).

Under continuous epidural anaesthesia and after cystoscopy a specially designed balloon (England *et al.*, 1973) tied over a Foley catheter was inserted into the bladder and inflated with saline by connecting the catheter to a standard intravenous drip set. The height of the drip bottle above the bladder was equivalent to the patient's systolic blood pressure which was measured at 15 min intervals. For the first 9 patients the balloon was inflated for 2 h but emptied for 5 min in each half-hour. For the rest of the series it was continuously inflated for 2 h. The volume to which the bladder was distended varied from 200 ml (a young girl) to 1600 ml (mean 857 ml). Following distension catheter drainage was maintained for about 48 h, after which the patient was discharged if otherwise fit.

Table 1 Effect of Distension on Symptoms. Forty-six Patients

Symptoms	*Types of instability*				*Totals*
	"Congenital"	*Late onset idiopathic*	*Neuropathic*	*Post-obstructive*	
Cured	1				1
Improved	1	1	1		3
Improved but relapsed	5	4	3	1	13
No change	5	14	5		24
Worse	1	4			5
	13	23	9	1	46

Results

Patients have been followed up for periods ranging from 9 to 37 months (average 27 months). Results have been assessed according to changes in symptoms, cystometry and complications.

Symptomatic changes following each patient's (46) initial distension are shown in Table 1. Only 4 patients have had any lasting improvement and all 4 have been followed for over a year. The duration of improvement reported by the 13 patients who later relapsed varied from 1 week to 8 months (average 9 weeks). Relapse is therefore unlikely to occur in the 4 patients reporting improvement or cure.

The 5 patients made worse were all female. Distension was one of a long series of attempts to improve their continence. Three have since undergone urinary diversion and the other 2 are coping with their symptoms.

Cystometry

Pre-operative cystometric studies have been performed on all patients and post-distension studies on 30 patients. There is not a single patient in whom we have objective evidence that uninhibitable contractions have been abolished. However, we have not performed post-operative studies on the 1 patient who was symptomatically cured, because she was only 13 years old, nor on 2 of the 3 who had permanent symptomatic improvement. The 1 patient with permanent symptomatic improvement who had had post-operative studies showed absolutely no change in her cystometry. Although we have not been able to demonstrate a return to normal cystometry, 5 of the 13 patients who later relapsed did show improvement; the intravesical pressure produced by their uninhibitable contractions was reduced by at least 25% during their period of symptomatic improvement.

Repeat Distensions

Ten of the 13 patients who had initial improvement with their first distension have had the procedure repeated following relapse of their symptoms. In only 2 cases was the symptomatic improvement repeated and neither of these 2 had any improvement in cystometry. When their symptoms recurred, distension was repeated a third time and finally failed to produce even symptomatic improvement in either patient.

Table 2 Complications of Bladder Distension

Complication	*No. of patients*
Ruptured bladder	1
Severe abdominal pain	1
Pyelonephritis	1
Anaesthetic complications	
Severe headache	2
Systemic absorption of epidural anaesthetic	1

Complications

Complications are shown in Table 2.

The ruptured bladder occurred in the last of 4 patients in whom the balloon was distended to a pressure of 20 cm of water above systolic blood pressure in order to compensate for the compliance of the balloon. The intraperitoneal rupture was repaired at laparotomy and the patient made an uneventful recovery.

Extraperitoneal rupture was suspected but not confirmed in the patient with severe abdominal pain; her pain subsided with conservative treatment. The other complications all responded to conservative measures.

Discussion

We had hopes for a satisfactory treatment for detrusor instability and have been disappointed that we have been unable to reproduce the encouraging results obtained in other centres (Ramsden *et al.*, 1976). A possible explanation is the use of continuous 2 h distension as opposed to 4 half-hour periods separated by 5 min with the balloon deflated. However, the first 9 patients in our series were treated by the interrupted method and only 1 obtained lasting benefit. This is not significantly different from the 3 patients who were permanently improved out of the 37 who had continuous distension. It is therefore unlikely that this point of technique accounts for our unsatisfactory results.

During the course of this series we wondered if we were inflating the balloon to a sufficiently high pressure. Laboratory tests were therefore conducted on a number of balloons and we found that an average pressure of 40 cm of water was required to overcome the elasticity of the balloon at a volume of 850 ml. As a result of these tests 4 patients had their bladders distended to a pressure of 20 cm of water above systolic blood pressure. Three were not improved and the fourth suffered a ruptured bladder. Subsequent patients were not distended above systolic blood pressure.

The incidence of complications is higher than the incidence of lasting improvement, even if the ruptured bladder is attributed to over-zealous technique. The incidence of deterioration in symptoms is also higher than the incidence of lasting improvement.

We have concluded that while over-distension may sometimes improve a patient's symptoms it does not convert unstable detrusor behaviour to stable function.

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An Objective Assessment of the Unstable Bladder of Psychosomatic Origin

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Summary—An objective assessment of 40 female patients with an unstable bladder was made. An organic or structural cause had previously been eliminated. In all patients an emotive or psychogenic origin for their urinary symptoms was discovered. The diagnosis of detrusor instability was confirmed by cystometry and bladder drill retraining was employed for 3 months. Cystometric investigation was then repeated and the patient was reassessed from the symptomatic point of view. The cure rate was 82.5%.

The unstable bladder in the context of this article refers to detrusor instability in which, as far as possible, an organic, infective or structural cause has been excluded. Eighty per cent of patients presenting at gynaecological out-patient clinics with symptoms of urge incontinence belong to this group.

In such cases the unstable bladder is of psychosomatic origin and the patient's symptoms have evolved as a result of an emotive or psychological disturbance (Frewen, 1972). The response to simple psycho-medical measures produced encouraging subjective results and these have been substantiated objectively by cystometry.

Patients and Methods

In order to evaluate the results of psycho-medical treatment only those patients with abnormal cystometry were included. The group consisted of 40 consecutive patients with a history of moderate or severe urge incontinence and with detrusor instability on cystometric investigation. Thirty patients were admitted to hospital for bladder retraining and the remaining 10 were treated as out-patients. Out-patient treatment in those with urgency of micturition as the predominant symptom and incontinence only occasionally is usually satisfactory. Bladder retraining can be successful only if the patient has a full understanding of the nature of her disorder and she is therefore issued on admission with a typescript on which is briefly explained the causation of her symptoms and how she can help to overcome them (Frewen, 1976). She is also given a micturition chart on which she records the times and intervals of urination, the volume of urine passed and the degree of incontinence present. The chart is a measure of her success in prolonging the intervals between voidings and the increase in her bladder capacity day by day. Supportive therapy is provided by the use of sedatives and by the anticholinergic group of drugs. The average length of stay in hospital for each patient was 10 days; they remained on treatment and were kept under surveillance for a period of 3 months. Each patient was seen at monthly intervals and a 30 min assessment was made of her progress. At the end of 3 months a repeat cystometric investigation was carried out and simultaneous pressure recordings were obtained from the bladder and the rectum either in the supine or erect positions.

Results

The criteria of cure were that within a period of 3 months from the onset of treatment the patient should be free of all abnormal urinary symptoms and the cystometric appearances should have returned to normal. Patients not fulfilling these criteria were regarded as failures.

Seven of 40 consecutive patients with urge incontinence associated with abnormal cystometry failed to respond to treatment or to fulfil the conditions of cure; the objective cure rate was therefore 82.5%. Examples of the response to

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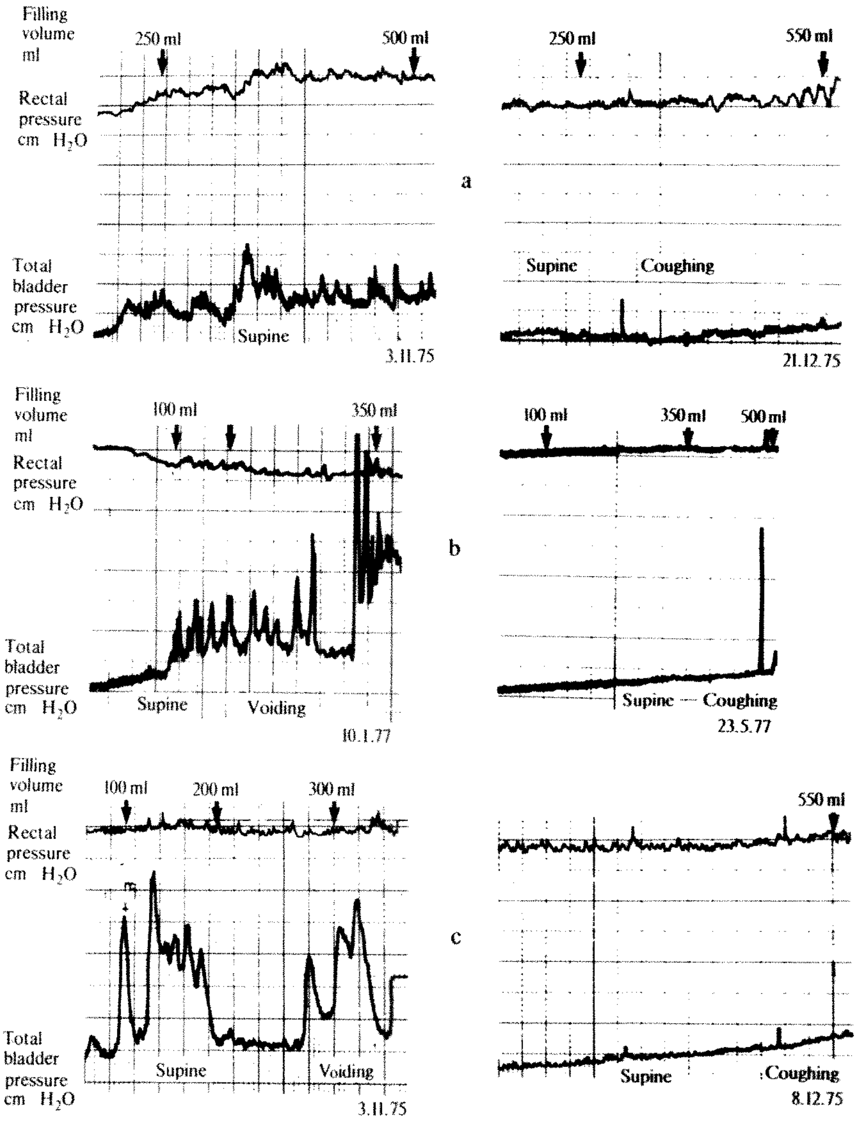

Fig. 1 Cystometry with a filling volume of 100 ml per min in 3 patients with urgency incontinence. (a) Patient's husband had carcinoma of the rectum and 2 of her brothers died from coronary thrombosis. The patient reacted with gross incontinence and nocturia. (b) An intelligent Indian patient who was completely unable to adapt herself to her new environment in England developed incontinence of urine within 6 months of her arrival. (c) A 36-year-old patient who had a morbid fear of surgery developed incontinence of urine 10 years ago following appendicectomy.

psycho-medical therapy in patients with severe detrusor instability are demonstrated in Figure 1.

In general, symptomatic cure antedated the return to normal cystometry by a period of 1 to 3 months so that cystometric surveillance in psychosomatic incontinence was performed at 3-monthly intervals.

Two patients with severe incontinence, low capacity bladders and high total bladder pressures are demonstrated in Figures 2a and b; in the second patient detrusor provocation was attained by a postural change (Fig. 2b). In Figure 2c the patient was free of all urinary symptoms and had normal cystometry after an interval of 15 months from the cessation of treatment.

The 7 patients who failed to respond to treatment were to some extent symptomatically improved, but on cystometric investigation their bladder instability showed little or no change. Five of them had chronically ill husbands and

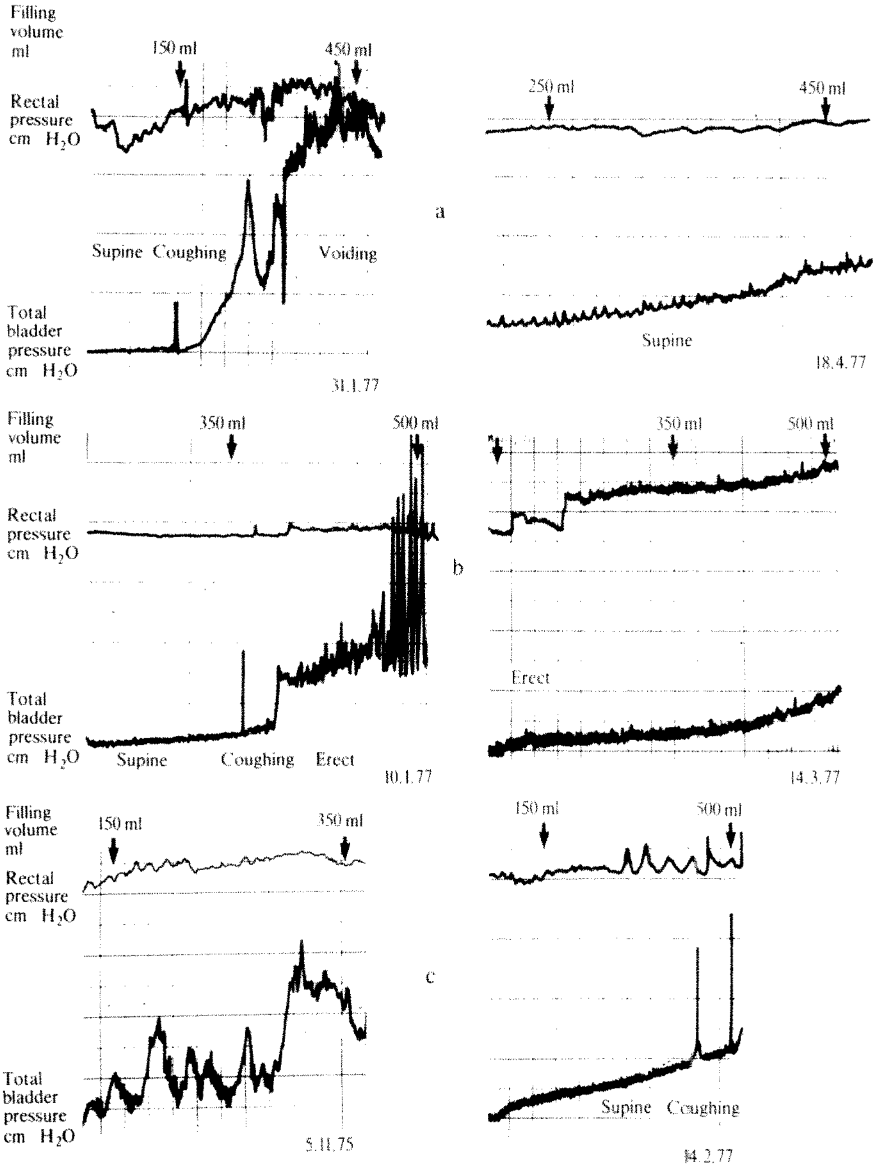

Fig. 2 Cystometry with a filling volume of 100 ml per min in 3 patients with urge incontinence. (a) A patient, aged 36 years, had had urge incontinence since she was 15 years old. She had been terrified of the dark since her early school days and her mother refused to give her a night-light. (b) The patient, her father and her child, were found to have pulmonary tuberculosis and as a result she had had urge incontinence for 10 years. (c) The patient's daughter, aged 17 years, had left home with an undesirable character. The daughter returned a year later and the patient's urinary symptoms rapidly disappeared.

were, as a result, under constant stress. One patient aged 77 years had had incontinence since the age of 7 years and another was awaiting divorce proceedings.

Discussion

The unstable bladder of functional origin is a frequent psychosomatic disorder and accounts for nearly one-third of all cases of incontinence of urine in women attending a gynaecological clinic. If no structural cause can be found for the unstable bladder the adoption of an instrumental or surgical approach is unlikely to be beneficial. Indeed, the results of urethral dilatation, bladder distension or denervation have on the whole been disappointing, or there has been only temporary success.

In general, the aetiology of psychosomatic incontinence is readily defined, although in some cases a searching history will be required before the emotive or psychogenic origin is elucidated. As the patients are always unaware of the cause of their symptoms it is essential that they have a clear understanding not only of the aetiology, but also of the relationship between the physical and psychological components of their urinary symptoms. Without this understanding, treatment is unlikely to be successful. Those who live in conflict with their environment or who are unable to adapt themselves to their social circumstances will not respond favourably unless their environmental conditions are remediable. This is well exemplified in 5 of the failed cases in which their environmental obligations, namely caring for their husbands with chronic illness, cannot at present be alleviated. It is doubtful whether, in the short term, such patients are amenable to any form of treatment. It is apparent, therefore, that the results of treatment in psychosomatic incontinence will be directly related to the conditions or influences under which the patient lives and the cure rate will be dependent to a significant degree on the successful re-orientation of the patient's way of life. If patients are cured symptomatically and uro-dynamically at the completion of 3 months' treatment they usually remain so, provided a further emotively traumatic event does not occur.

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Biofeedback in the Treatment of Detrusor Instability

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Summary—Detrusor instability has remained resistant to conventional forms of treatment. An attempt to use biofeedback methods in its management is described. Six female patients with symptoms of frequency, urgency and urge incontinence due to detrusor instability were conditioned to auditory and visual stimuli for 6 to 8 1 h sessions. They were assessed clinically and urodynamically. The results are presented as well as detailed case studies of 3 patients. Subjectively, 3 were cured, 2 improved and 1 remained the same; objectively, 3 were cured, 1 improved and 2 remained the same. No significant side effects were encountered.

Urinary incontinence, urgency and frequency, associated with detrusor instability are distressing complaints both to the patient and to the doctor as they are often resistant to the more usual forms of treatment such as surgery and drugs. Frewen (1972) suggests that urge incontinence, which may be due to detrusor instability, is a psychosomatic disorder in which emotional factors play a predominant role.

Biofeedback training is a form of learning or re-education in which the patient is placed in a closed feedback loop where information about 1 or more of her normally unconscious physiological processes is made available to her as a visual, auditory or tactile signal (Stroebel and Glueck, 1973). It has previously been used to treat other disorders of autonomic function with moderate degrees of success. These include hypertension (Love *et al.*, 1974) and longstanding faecal incontinence (Engel *et al.*, 1974). Its successful use in a female patient with hysterical urinary retention was described by Stanton (1976).

In this ongoing study, biofeedback training was used to re-educate female patients with urinary symptoms associated with detrusor instability, in order that these symptoms might be alleviated.

Method

Patients in this study were diagnosed on video-cystourethrography (VCU) (Bates and Corney, 1971) as having detrusor instability if a detrusor pressure rise of more than 15 cm of water was recorded during any of the provocative tests. These included fast bladder filling, coughing during filling, standing up and coughing when erect. Cystoscopy was performed to exclude organic bladder pathology and a neurological opinion was sought to rule out any occult neurological lesion.

When the patient attended for the first session of biofeedback training the procedure was explained to her and she was put at her ease as much as possible. Using a clean procedure, 2 catheters were introduced into the bladder; a 14 F.G. urethral catheter was used for filling and a 1 mm fluid-filled catheter measured the total bladder pressure. A 2 mm fluid-filled catheter, protected from faecal blockage by a finger stall, was introduced into the rectum to measure the rectal pressure which was taken to be equivalent to the abdominal pressure. The rectal pressure was electronically subtracted from the total bladder pressure to give the detrusor pressure and all 3 parameters were recorded on a chart recorder (Fig. 1). A voltage to frequency converter was connected to the detrusor pressure strain gauge amplifier, which emitted an auditory signal. The gain and frequency range of this could be altered to suit the individual patient but once a baseline tone was decided upon, the note emitted through the loudspeaker increased in pitch as the detrusor pressure rose, and decreased as the pressure fell. Thus a patient with an unstable detrusor would hear a rise in pitch as the detrusor pressure increased. A mirror was positioned in such a way that the patient, lying supine, could look into it and see the detrusor pressure pen deflection.

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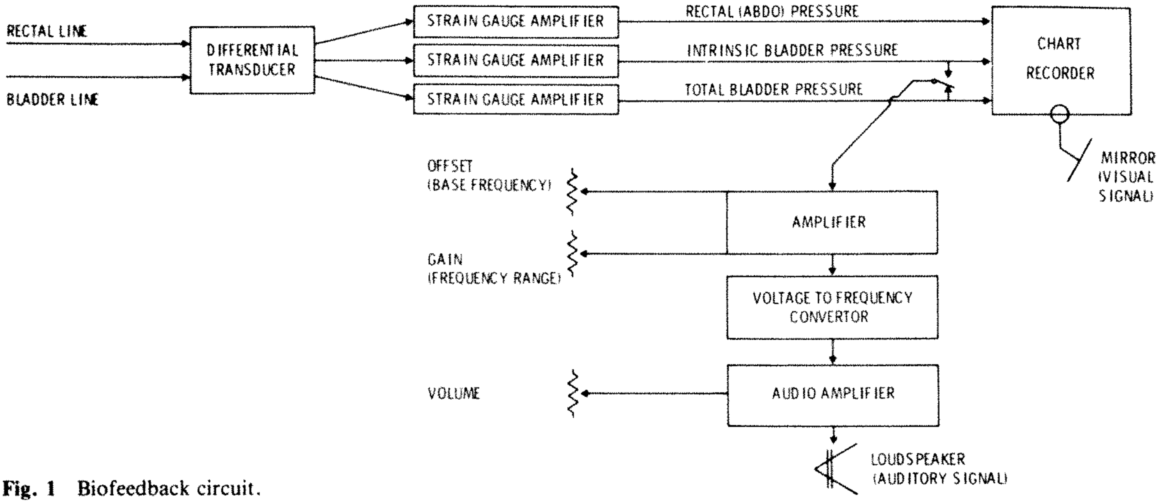

Fig. 1 Biofeedback circuit.

With the patient lying comfortably, bladder filling was commenced using 0.9% saline, prewarmed to body temperature, at a rate of 100 ml per min. The patient was asked to listen to the auditory signal and to watch the chart recording and to say when she had the first sensation of desire to void and again when her bladder was absolutely full. She was also asked to notify the attendant if she leaked.

When full capacity was reached the bladder was emptied and filling was recommenced at a slower rate; this time the patient was asked to try to control the rise in pitch of the auditory signal by concentrating, deep breathing, fist clenching, general relaxation or any other method which she found helpful. This varied from patient to patient, some preferring to talk, others finding that tightening certain muscle groups helped. When the bladder was full it was again emptied. Each session was planned to last about an hour, during which time the bladder might be filled 2 or 3 times, depending upon the rate of filling. Most patients attended for about 6 to 8 sessions at weekly intervals and as they became used to the training and were better able to control the pressure rise on filling, provocative tests such as laughing, tap running, standing up with a full bladder and coughing when erect were used.

Between sessions the patient was asked to keep a "urinary diary" in which she recorded the number of "urges" to void during each day and whether or not she was incontinent at any time. She also kept a record of her urinary frequency. Patients were encouraged to void only when absolutely necessary. Subjective improvement was recorded week by week as the treatment progressed and at the end of treatment a further videocystourethrogram was performed, as was a Urilos Nappy Test (Stanton and Ritchie, 1977) to assess the patient's objective improvement. Midstream specimens of urine from all patients were sent regularly for culture and sensitivity.

Results

To date 6 female patients have been treated and have completed 3 months' follow-up. Their average age was 39 years (range 22 to 47 years). A patient is thought to be subjectively cured if she no longer complains of frequency, urgency or urge incontinence. Frequency is taken to be the passage of urine 7 or more times during the day and twice or more at night. An objective cure exists if the patient no longer exhibits detrusor contractions at any time during cystometry, the detrusor pressure does not rise above 15 cm of water and the patient does not leak at any time. Using these criteria the results are shown in Table 1. Only 1 of the 6 patients failed to respond and she has since been referred to the psychiatrists after an attempted suicide.

Table 1 Preliminary Results—6 Patients

	Subjective	*Objective*
Cured	3	3
Improved	2	1
Failed	1	2

Table 2 Subjective Changes—6 Patients

Symptoms		*Before treatment (No. of patients)*	*After treatment (No. of patients)*
Frequency:	diurnal	6	2
	nocturnal	5	1
Urgency		6	2
Urge incontinence		5	2

Table 2 shows the symptomatic changes. If frequency is assessed as the number of times micturition occurs, then prior to treatment the mean diurnal frequency was 15.7 (S.D. = 5.2) and the mean nocturnal frequency was 1.8 (S.D. = 1.2). After treatment these figures were reduced to 5.5 (S.D. = 2.4) and 0.3 (S.D. = 0.5) respectively.

Table 3 Objective Changes—6 Patients

VCU	*Before treatment*		*After treatment*	
	Mean	*(S.D.)*	*Mean*	*(S.D.)*
First sensation (ml)	143	(83)	156	(82)
Capacity (ml)	405	(67)	467	(52)
Pressure rise on filling (cm H_2O)	28	(25)	25	(26)
Pressure rise on standing (cm H_2O)	18	(10)	2	(4)
Detrusor contractions + leakage of urine	5 patients		2 patients	

The objective changes are shown in Table 3. The change in mean total detrusor pressure rise (the pressure rise on filling plus the pressure rise on standing) was 46 cm H_2O to 27 cm H_2O. If, however, the 2 patients who failed objectively are excluded, then the mean total detrusor pressure rises before and after treatment are 33 cm H_2O and 13 cm H_2O respectively. At VCU prior to treatment 5 of the 6 patients exhibited detrusor contractions with simultaneous leakage of urine; after treatment only 2 did. No urinary tract infections were encountered.

The case studies of 3 of the patients are presented in detail:

Case 1

Mrs I. B. (age 47 years) presented with a history of 14 years' incontinence which was worsening. She complained of stress incontinence, urgency and urge incontinence, and also of frequency, micturating 8 times during the day and 3 times at night. Videocystourethrography showed a first sensation at 110 ml and a bladder capacity of 400 ml with a pressure rise on filling of 10 cm of water and on standing of 12 cm of water. She had detrusor contractions up to 36 cm of water following coughing and exhibited stress incontinence. Initially she was treated unsuccessfully with Urispas 200 mg qds. Two months later she started biofeedback training. She was given 7 sessions, during which time she gradually improved. At the end of this time she voided only 3 times during the day and not at all at night and was no longer incontinent. Follow-up videocystourethrogram showed a first sensation at 180 ml and a bladder capacity of 500 ml. Her pressure rise on filling was 7 cm of water and on standing 1 cm of water. There were no detrusor contractions. Slight stress incontinence was noted but the patient was not concerned about this. The Urilos Nappy Test was negative. At 3 months' follow-up the situation was unchanged.

Case 2

Mrs J. S. (age 42 years) complained of stress incontinence and frequency, micturating 15 times during the day but not at all at night. Her initial videocystourethrogram showed a pressure rise on filling of 8 cm of water and on standing of 16 cm of water. She also exhibited stress incontinence. After 6 sessions of biofeedback she was greatly improved; she was never incontinent and micturated only 6 times during the day. Follow-up videocystourethrogram showed a pressure rise of 4 cm of water on filling and no pressure rise on standing. Stress incontinence was not present during the test nor during the Urilos Nappy Test. She remained the same when seen at 3 months' follow-up.

Case 3

Mrs A. J. (age 22 years) complained of increasing frequency of micturition for the last 2 years. She said she voided up to 20 times during the day and 3 times at night. Videocystourethrogram showed a first sensation at 25 ml and a capacity of 400 ml with a pressure rise of 18 cm of water on filling and 6 cm of water on standing. She leaked urine on standing and on coughing. At first she was very apprehensive about biofeedback training, but after 8 sessions she said that she micturated only 4 to 5 times during the day and not at all at night and that she was never incontinent. Videocystourethrography showed that she still had a pressure rise on filling of 19 cm of water but no pressure rise on standing. Her first sensation was at 75 ml and capacity 500 ml. Stress incontinence did not occur on this occasion nor on Urilos Nappy Test. When seen at 3 months' follow-up she was symptomatically cured.

Discussion

Many forms of treatment have been tried in the hope of finding a cure for detrusor instability. This in itself indicates that none is completely successful. Surgery originally aimed at denervating the bladder (Ingelman-Sundberg, 1959) but this did not produce lasting improvement. Sacral neurectomy was tried (Torrens and Griffiths, 1974) but was found to be successful only in carefully selected cases. Beck *et al.* (1976) postulate that abnormal bladder neck funnelling may cause detrusor instability in some women and by surgical correction of this fault they have obtained a cure in about 50% of their cases and an improvement in 77%. However, they recommend surgery only as a last resort in the treatment of detrusor instability. More recently cystodistension (Dunn *et al.*, 1975) has been attempted, and as yet the long-term results of this form of treatment are unknown. It does, however, have a risk of bladder rupture.

Drug therapy is still the mainstay of treatment in this condition and it, too, is unsatisfactory in many cases. The drugs in common use try to control uninhibited detrusor contractions either by direct anticholinergic activity or by stimulating the beta-adrenergic receptors (Moolgaoker *et al.*, 1972; Brown *et al.*, 1973; Stanton, 1973). Bladder drill and supportive psychotherapy have been attempted (Frewen, 1978) and the results of this non-invasive treatment are promising.

Biofeedback treatment avoids the morbidity of surgery and the side-effects of drug therapy, but it does hold certain problems of its own. There is a risk of urinary tract infection, although we have not yet encountered this. Some patients find the sensation of catheterisation unpleasant and others are resistant to the implication that their urinary problem might be psychosomatic. The treatment involves several visits to the hospital, and this is reflected in about a 15% incidence of failure to attend for sessions. In assessing the "cost-effectiveness" of this technique, account must be taken of the need for both a doctor or highly trained nurse and technician to be present during most of the training time.

It is interesting to note that although not all of the patients have been cured, or even improved, by biofeedback training, frequency was universally less after treatment. Possibly this is due to the patient's greater awareness, brought about by the use of the urinary diary.

It is concluded that the successful treatment of urological symptoms associated with detrusor instability by biofeedback methods and its lack of complications are shown in this preliminary report. Although only 6 patients have completed treatment and 3 months' follow-up, others are currently undergoing treatment. In view of the modest success achieved by other forms of treatment, some of which have a significant morbidity, we feel that biofeedback methods of therapy should be evaluated further.

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Ultrasonic Lithotriptor for Urethral and Bladder Stones

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Summary—Bladder or urethral calculi in 50 patients were effectively fragmented and removed per-urethrally using an ultrasonic lithotriptor with the probe vibrating at 30,000 impulses/s. In adults, local anaesthesia was employed and the operation performed as an out-patient procedure. The method has the advantages over others discussed in that a small (23 F) sheath is used and that damage to the bladder or urethra by the probe is avoided. Using a newer, modified sheath resembling that for punch prostatectomy, larger stones can be fragmented by engaging the stone in the fenestrum of the sheath.

Stones in the bladder and urethra, in both children and adults, have long been a major urological problem in Arabia and their treatment has been well described by Rhazes (AD 850-923), Hali Abbas and Avicenna (AD 980-1037). Abulasis (AD 936-1013) described crushing stones; if the stone was large or irregular he advocated the use of the michab, an instrument which was passed up the urethra and drilled the stone into fragments which were subsequently washed out by the passage of urine. Over the past few centuries there has been little advance in the treatment of these stones and even now an occasional lithotomist can be found practising the technique of Frère Jacques (1651-1714).

Open operation, whether in the bladder or urethra, has the disadvantages that it requires hospitalisation and usually general anaesthesia. The classical blind lithotrite can damage the bladder wall, especially in the hands of the less experienced surgeon, and may also require multiple sessions. Cystoscopic litholapaxy is limited by the size of the stone which can be grasped and visualisation may become difficult if bleeding is encountered. Neither the blind nor the cystoscopic lithotrite can destroy stones impacted in the urethra.

The 2 electronic lithoclasts, the Urat and the prototype British model, have been claimed to be safe, provided the discharge does not come into contact with the bladder wall (Reuter, 1970; Wallace *et al.*, 1972). However, recent animal work has shown that perforation of the bladder can occur easily and, even more serious, rupture of the gas-filled small intestine can also be caused by this type of electrical discharge (Tidd *et al.*, 1976). The electronic lithoclast, using a flexible electrode in the ureter, can drive fragments of stone through the ureteric wall and even rupture the ureter (Hall, 1973).

During the last 6 months at the Central Hospital, Riyadh, an ultrasonic lithotriptor, designed by Professor Lutzeyer of Aachen and manufactured by Storz, has been used on bladder and urethral stones. The apparatus consists of a conventional cystoscope, sheath size 23 F, through which an angled Hopkins telescope and the ultrasonic probe can be inserted. The probe is hollow so that by applying suction the stone can be held in apposition with the serrated teeth of the probe. Twin pedals control the ultrasonic generator and the suction; either or both can be activated at will.

There has recently been developed a new sheath, shaped like a punch resector, with which the stone can be engaged in the fenestrum of the sheath and the probe used to nibble it away.

Clinical Material

During a 6-month period since October 1976, 50 patients with single or multiple bladder stones or urethral stones have been treated with the lithotriptor. The majority have been treated under local anaesthesia and on an out-patient attendance. None were in the prostate age group nor did any have stricture or bladder neck obstruction. Two patients were paraplegic.

Children under the age of 12 have been

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admitted to hospital and an infant lithotrite used to crush the stones under a general anaesthetic. In 2 patients an open cystotomy was performed because in 1 a corrugated drain and in the other 6 inches of Foley catheter formed a stone nucleus.

Results

In all patients the stones were completely crushed in 1 or at most 2 sessions. One patient was treated by combined lithotripsy and blind litholapaxy because of bleeding. No damage was produced to the bladder or urethra even when the stone was treated in the urethra. Drilling of a urethral stone is considerably easier than drilling of a comparable stone in the bladder since the stone is gripped by the urethral musculature.

The advantages claimed for the ultrasonic lithotriptor technique are as follows:

1. Since its calibre is only 23 F the sheath can be used with all standard Storz equipment and can be passed in adults and in some adolescents under local anaesthesia.
2. The ultrasonic probe is vibrating at 30,000 impulses per/s and cannot harm the muscle or mucosa of the bladder wall. This can be proved by touching the end of the probe with a bare finger, when no damage or discomfort will be experienced.
3. Since the destruction of the stone is effected by vibration rather than explosion there is no risk of stone fragments being driven into the bladder wall.
4. The use of a lithotriptor in the urethra is facilitated by the stone being gripped by the urethral muscle.
5. In many patients the procedure can be carried out under local anaesthesia and at an outpatient attendance.
6. Using the new, modified sheath, larger stones can be nibbled by engaging the stone in the fenestrum of the sheath. Stones up to 6 cm in diameter can be destroyed using the suction technique alone.
7. In European centres, where relatively few stones are seen in younger patients, the cost effectiveness of such equipment may be argued. In Middle East centres, where 1 or 2 patients with calculi may be seen every week, the saving in beds, hospitalisation and theatre time is considerable.

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Endourethral Urethroplasty: A Simple Method for Treatment of Urethral Strictures by Internal Urethrotomy and Primary Split Skin Grafting

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Summary—Primary endourethral split skin grafting was performed in 4 patients operated upon for stricture of the bulbous urethra by internal urethrotomy. Post-operatively, all grafts were found to have taken. Follow-up has ranged from 4 to 12 months. The results were considered good in all patients and after release from the hospital they had no subjective symptoms. Further urethral dilation has not been necessary in any of the patients.

Internal urethrotomy has been used for a long time. A lancellated catheter was used by Ambroïse Paré (1510-1590) and through the years the technique has been modified. The ingenious urethrotome described by Otis (1878) is still in use in many centres 100 years after its introduction. This blind technique was later replaced by internal urethrotomy under direct vision (Helmstein, 1964; Sachse, 1974). Although many authors have had good results with the procedure (Wise *et al.*, 1972; Carlton *et al.*, 1974; Sachse, 1974; Matouschek and Michaelis, 1975) others give the method a limited place as it seldom, if ever, leads to a permanent cure of a stricture (Blandy *et al.*, 1976).

At internal urethrotomy, the incision is left to heal by "second intention". This involves formation of new scar tissue which in time may contract, resulting in recurrence of the stricture. One method of diminishing scar tissue formation after an incision is primary skin grafting.

This paper presents a method for treatment of urethral strictures by internal urethrotomy in combination with primary endourethral split skin grafting. Preliminary results of the method have been reported previously (Pettersson and Lundstam, 1977).

Patients and Methods

Clinical

During a 12 month period, 4 men were treated by endourethral urethroplasty (EUUP) for strictures of the bulbous urethra (Table 1). Three patients presented with acute urinary obstruction (Nos. 1, 3 and 4) and 1 complained of poor stream (No. 2). Two had suffered from recurrent epididymitis (Nos. 1 and 2). The duration of symptoms ranged from 1 to 12 years. One patient (No. 3) had had intermittent bouginage every 6 to 8 weeks for 12 years. Ordinary internal urethrotomy was tried first but the stricture recurred within 3 months. Endourethral urethroplasty was performed 9 months later.

Table 1 Patients Treated by Endourethral Urethroplasty

Patient No.	*Age (years)*	*Symptoms*	*Duration of symptoms (years)*	*Treatment before EUPP**
1	24	Acute retention Urinary infection Epididymitis Prostatic calculi	7	Bouginage
2	29	Poor stream Urinary infection Epididymitis	5	-
3	77	Acute retention	12	Bouginage Internal urethrotomy
4	57	Acute retention	1	Bouginage

* EUPP = endourethral urethroplasty.

Prior to treatment, a quantitative urine culture and a retrograde urethrogram were obtained.

Operative Procedure

The operation was performed under general or

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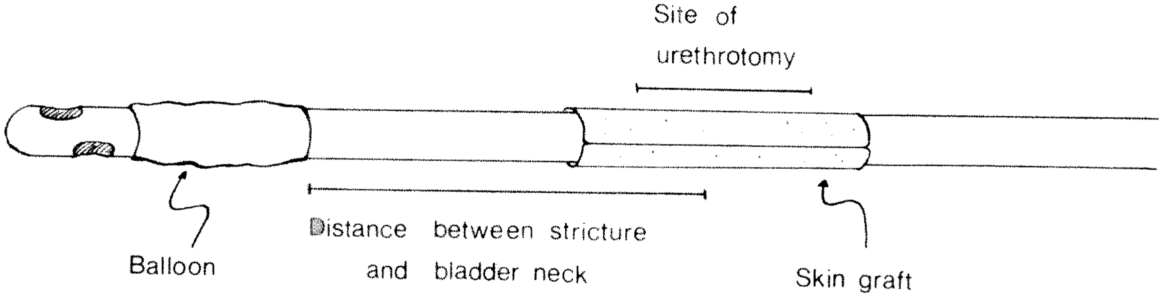

Fig. 1 Schematic drawing of a silastic Foley catheter. The split skin graft is glued with the epithelial surface towards the catheter. The position of the graft was calculated from the pre-operative urethrogram and transferred to the catheter, measured from the lower edge of the balloon. Note the graft surplus as compared to the length of the incision.

spinal anaesthesia. The urethrotomy was performed with a Winter-Ibe urethrotome under direct vision. The incision was made at 12 o'clock and was carried down until all fibrous tissue was incised and until the urethrotome (20 F) passed easily. A split skin graft (thickness 0.45 mm) was cut with an electric dermatome from the thigh. The graft was made about 2 cm longer than the length of the urethral incision. The breadth was 20 mm, *i.e.* equal to the circumference of a 20 F catheter. The distance between the bladder neck and the centre of the stricture was measured on the urethrogram (lateral projection) and corrected for enlargement. The calculated distance was marked out on a silastic Foley catheter (20 F), as measured from the lower edge of the balloon (Fig. 1). The graft was centred to the obtained mark and, with the epithelial surface towards the catheter, glued (Arasol, Röhm Pharma, Darmstadt) around the catheter, which was to serve as a splint. As soon as the glue had set, the catheter was inserted into the urethra, the balloon inflated, and the catheter withdrawn until the lower edge of the balloon reached the bladder neck. A firm, well-padded compression dressing of voluminous gauze and elastic adhesive was applied to the perineum and the urethra (Johanson, 1953). The bladder was drained by a suprapubic cystostomy.

Post-operative Care

The dressing was retained for 6 days, during which time the patient remained supine in bed. The urethral catheter was removed after 10 days, when the glue was considered to have dissolved. After about 2 weeks, urethroscopy was performed to check the graft. The cystostomy was retained for 4 to 6 weeks. Before the cystostomy was removed, a voiding urethrogram was obtained. All patients were given antibiotics. To prevent thrombosis 500 ml dextran 70 (Macrodex$^{(R)}$, Pharmacia) was given during the operation and every second day post-operatively for 6 days.

Follow-up Studies

The patients were observed at 3, 6, 9 and 12 months post-operatively. The evaluation consisted of quantitative urine culture, urine flow rate, retrograde urethrogram and urethroscopy including intraurethral photography. The patients were also questioned with regard to subjective symptoms such as frequency, pain, voiding stream, and sexual function.

Results

Adequate follow-up data are available in all 4 patients. The time since operation ranged between 4 and 12 months (Table 2). The results were considered good in all patients and after release from hospital they had no subjective symptoms.

Table 2 Results of Endourethral Urethroplasty

Patient No.	*Observation time (months)*	*Timed micturition (sec 0.100 ml^{-1})*	*Minimum diameter on urethrogram (mm)*	*Urinary infection*
1	12	9	5	+
2	9	3	7	–
3	5	6	8	–
4	4	6	6	–

Further urethral dilatation was not necessary in any patient.

At urethroscopy, 2 weeks post-operatively, all 4 grafts were found to have taken. Around the oval centre of the graft necrotic remnants of the

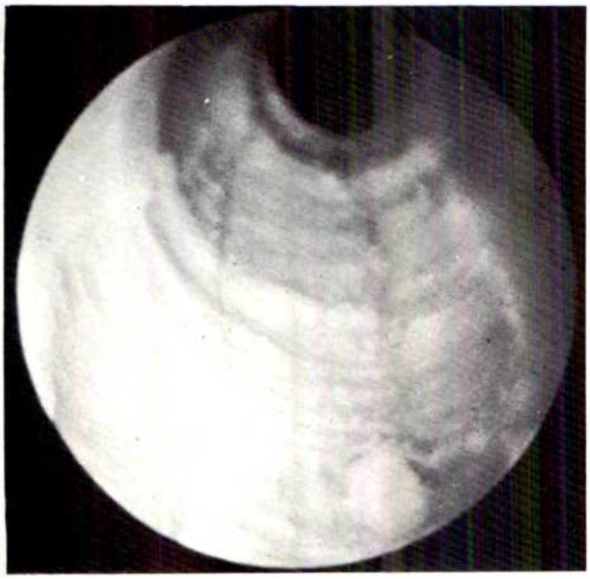

Fig. 2 An intraurethral photo of a graft 3 months postoperatively (Patient No. 3). The surplus had been shed and the graft had assumed its final oval shape and pale yellow colour.

graft surplus were seen. At the next endoscopic examination, 3 months after the operation, the surplus had been shed (Fig. 2). At this time, the graft had assumed its final oval shape and pale yellow colour which it preserved during the whole of the follow-up period. In 3 patients (Nos. 2, 3 and 4) a 20 F urethroscope passed the graft without difficulty. In 1 patient (No. 1), the urethral lumen was slightly decreased at the proximal border of the graft. A 17 F urethroscope, however, passed easily.

The urine flow rate was within normal limits by the time the suprapubic catheter was removed. Table 2 shows the results of timed micturition obtained at the last post-operative evaluation. The values were within normal limits.

The post-operative urethrogram showed a considerably increased urethral diameter at the site of the former stricture as compared with the preoperative examination (Figs. 3 and 4). The minimum diameter, as measured from the last postoperative urethrogram, is given in Table 2. Three patients (Nos. 1, 2 and 3) had had recurrent

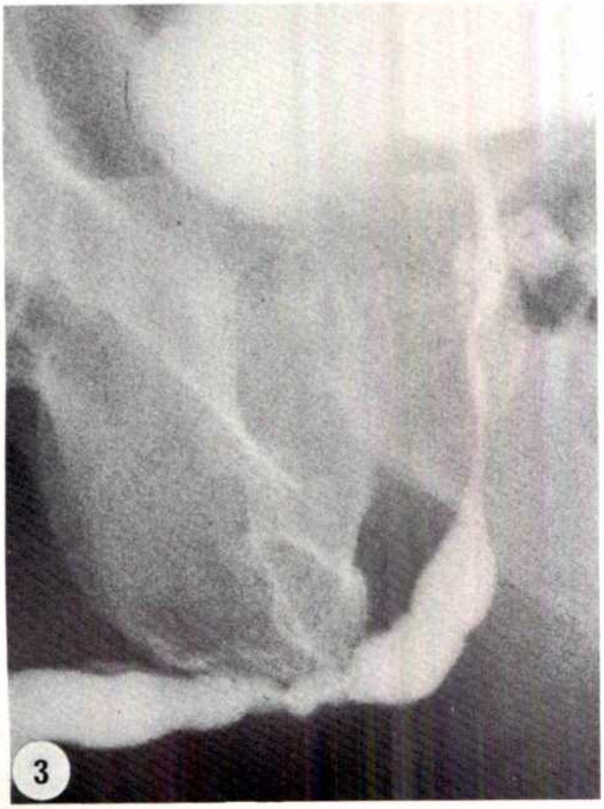

Fig. 3 Pre-operative urethrogram of a bulbous urethral stricture (Patient No. 3).

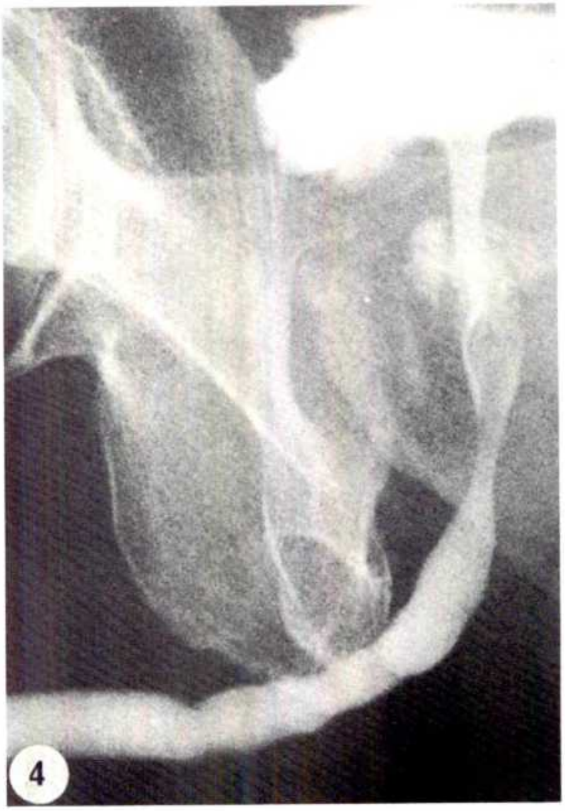

Fig. 4 Post-operative urethrogram obtained 6 months after endourethral urethroplasty (Patient No. 3).

urinary tract infection pre-operatively (Table 1). In 1 patient (No. 1), the infection recurred post-operatively; the other 2 had negative cultures (Table 2).

Few complications were encountered. Patient No. 1 underwent surgery again 3 days post-operatively due to haemorrhage caused by the percutaneously performed cystostomy. A few weeks later, he had egg-shell-like calcifications from the catheter crushed and evacuated trans-urethrally. No other complications were encountered.

Discussion

Four patients were operated upon for stricture of the bulbous urethra by internal urethrotomy in combination with primary endourethral split skin grafting. Post-operatively, all grafts were found to have been successful. No sign of recurrence of the strictures was encountered.

The actual procedure is an application on urethral strictures of the original Nové-Josserand (1919) operation for repair of hypospadias. According to his method, a skin graft was coiled round a probe which was introduced through a subcutaneous tunnel on the ventral aspect of the penis. It should be noted, however, that the whole circumference of the urethra was replaced by this method and that the operation was not performed endourethrally.

To some extent, conventional internal urethrotomy may be compared with a traumatic urethral lesion. The amount of scar tissue that follows the incision will depend mainly on whether infection supervenes or not. Infection can prevent the normal migration of epithelial cells or even cause their regression. The excess of granulation tissue which ensues in badly infected wounds contributes to excessive scarring. From experimental studies in the rat, Singh and Blandy (1976) concluded that the post-traumatic inflammatory reaction in the urethra was much more severe when extravasation of urine was not prevented. To reduce the inflammatory reaction after internal urethrotomy, a urethral catheter is often left indwelling for 3 weeks (Katz and Waterhouse, 1971) or longer (Engel *et al.*, 1972; Wise *et al.*, 1972). Despite the deviating function of a urethral catheter, it is nevertheless difficult, if not impossible, to avoid secondary urethritis and infection of the urethrotomy when the urethra is left intubated for several weeks. Another proposed method of reducing the inflammatory reaction in connection with treatment of urethral strictures is the use of steroids administered systemically (Roald, 1955) or injected *per urethram* (Hebert, 1972). The post-operative inflammatory reaction and scarring tendency, however, may be reduced to a minimum by obtaining conditions for primary healing. This may be achieved by primary skin grafting.

The actual graft position on the catheter, which corresponds exactly to the urethrotomy, cannot be given with the present technique. It is, therefore, not possible to use a graft which precisely fits the incision. However, as a skin graft will take only on incised tissue and not on intact urethral epithelium, it may be applied in excess, which reduces the need for accuracy in its application. The graft surplus will necrose and later be shed. As this takes place more rapidly with a thin graft as compared with a full thickness graft, a split skin graft was chosen. When split skin grafts are used, on the other hand, there is a risk of secondary contraction of the graft (McCormack, 1954). The tendency to contract, however, has been considered much less pronounced when a thick split skin graft is used (McCormack, 1954).

The results of the procedure were evaluated on the basis of a urine flow rate, urethrograms and endoscopic examinations. Urine flow rate is considered a functional evaluation of the results of urethral stricture repair. It is sufficiently accurate and has the advantage that it can be performed by the patient at home using a stopwatch and a graduated glass. As pointed out by Lapides and Stone (1968), a retrograde urethrogram can delineate most small diameter strictures of the anterior urethra, but strictures of a calibre greater than 20 F are not readily identifiable. Urethrography is, therefore, considered suitable to exclude recurrence of a stricture but is less exact in the grading of a good result after urethroplasty. Urethroscopy with photographs of the urethra offers objective evidence of the results. The easy passage of a former stricture with an instrument of a given calibre provides a modified urethral calibration.

So far, the results of the procedure have been encouraging, but the observation time of 4 to 12 months is short and the number of patients too small to permit definite evaluation of the results. Nevertheless, the procedure is easy, it may be performed under local anaesthesia, and the method does not render other reconstructions more difficult if it should fail.

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The Mucosal Electrosensitivity Threshold (MST): A Test for use in Conjunction with Electronic Stimulation in Urinary Incontinence in Women

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Summary—A new test to select those patients most likely to respond to electronic stimulation of the pelvic floor muscles is described.

Electronic stimulation of the pelvic floor muscles is a convenient and safe method of treating urinary stress incontinence. Unfortunately, a number of patients do not seem to respond. Doyle *et al.* (1974) treated 130 patients with the vaginal tampon electrode, the anal plug, or the electronic Hodge pessary and reported an overall success rate of 40% in an unselected group.

Over the last 5 years we have achieved a success rate of 82% in 28 patients (Kiesswetter and Flamm, unpublished data).

In this preliminary study we measured the MST of the rectum in males, and the vagina in females. We defined this threshold as the voltage amplitude required for sensation of the stimulus to be perceived.

Methods and Results

We tested the MST of the rectum and vagina in 198 unselected male and female patients. The stimulus used has a rectangular pulse of 0.2 msec duration, with a frequency of 180 cycles/s and an amplitude of 0 to 7.5 V with one 9 V battery used, or 7.5 to 15 V with 2 batteries.

Of all the patients tested, 73% had rectal sensation at the lower range, but only 38.8% of the women had vaginal sensation when using this 7.5 V stimulus, the output expected from commercial devices. On increasing the amplitude to 15 V, we found that an additional 15.6% had rectal sensation and an additional 36.4% vaginal sensation; 10.6% had no rectal sensation and 25.5% no vaginal sensation even with the 15 V stimulus. The results of this part of the study are shown in Figure 1.

We then examined the vaginal and rectal MST in 41 stress incontinent females; some of these had had previous surgery and others had not. We found that 65.8% had rectal sensation with the 7.5 V stimulus, while 34.1% experienced vaginal sensation. Increasing the stimulus to 15 V improved these figures by 17% and 31.7% respectively; 17% of these patients experienced no rectal sensation and 31.7% no vaginal sensation. Previous vaginal repairs did not necessarily alter the electrosensitivity of the mucosa. Our results are shown in Table 1.

A comparison of the MST in overweight and normal weight patients did not show a significant difference between either group.

Table 1 Female Stress Incontinence Mucosal Sensory Threshold to Electrical Stimulation

	Rectum			*Vagina*		
	(1)	(2)	(3)	(1)	(2)	(3)
No previous surgery n = 16	12	2	2	6	4	5
After vaginal repairs n = 25	15	5	5	8	9	8
Total n = 41	27	7	7	14	13	13
Percentage	65.8	17.0	17.0	34.1	31.7	31.7

(1) 0 to 7.5 V: output of commercial stimulators powered with 1 9 V battery.
(2) 7.5 to 15 V: 2 9 V batteries (pulse generator).
(3) No sensation at all.

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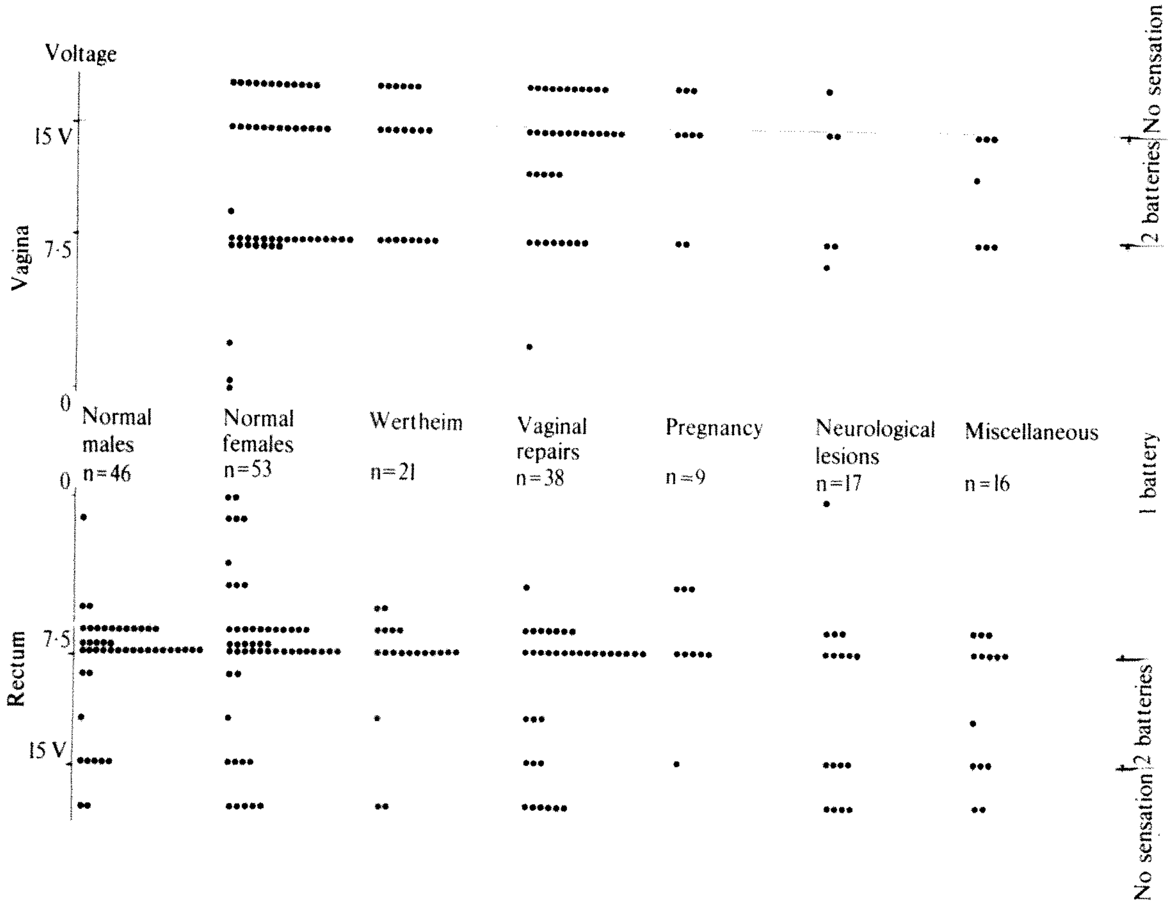

Fig. 1 Mucosal sensory threshold to electrical stimuli on rectum and vagina.

Discussion

It has been suggested by Trontelj *et al.* (1974) and Godec *et al.* (1976) that the therapeutic effect of external reflex stimulation by electronic means depends to some extent on the excitation of exteroceptive segmental receptors.

We have assessed the MST of the rectal and vaginal mucosa in nearly 240 patients. From the information gained in this study it is now our policy to select for electronic treatment only those incontinent women whose MST test is positive. We feel that the application of this criterion improves our results considerably, and our final correlations will be presented in a subsequent communication.

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Technique and Results of the Colonic Conduit, Continent by Means of a New Magnetic Stoma Seal An Experimental Study

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Summary—On the basis of satisfactory results with a new magnetic stoma seal in colostomy patients this seal, consisting of a magnetic ring and cap, was used in an experimental study to convert the colonic conduit into a continent reservoir.

Complete continence was obtained in all of the 12 animals which survived the operation. All rings were well accepted by the tissue when the procedure was staged by implanting the ring transperitoneally several weeks prior to fashioning of the conduit.

Residual urine was low, owing to an ideal energy-balance pattern. Coloureteric reflux was successfully prevented in all cases where a long-tunnel-modification of the Leadbetter-Clarke technique was used. Hyperchloraemic acidosis and deterioration in renal function were not observed. All conduits were infected.

Late results of the ileal conduit have been disappointing and some urologists now prefer the colonic conduit for urinary diversion in the patient with long life expectancy (Altwein and Hohenfellner, 1975; Mogg, 1975; Schwarz and Jeffs, 1975; Shapiro *et al.*, 1975; Hendren, 1976). Feustel *et al.* (1976) have recently developed a new magnetic stoma seal for colostomy and ileostomy patients (Fig. 1), which has been applied in over 100 patients with reasonable success. This seal seems to be suitable for converting the colonic conduit into a continent reservoir. This view is supported by experience with colocystoplasty, coloprostatoplasty and colourethroplasty, where a segment of colon may well serve as a bladder substitute with excellent long-term results.

In order to study the problems of this procedure, a continent colonic conduit was constructed in 16 dogs.

Material and Methods

Sixteen female mongrel dogs with an average body weight of 22.5 kg were anaesthetised with Pentothal and were intubated. Pre-operatively they had been kept for 3 days on clear liquids enriched with sugar. During the operation they received 1000 ml of 5% glucose, 500 ml of 0.9% NaCl and 500 ml of 6% Dextran.

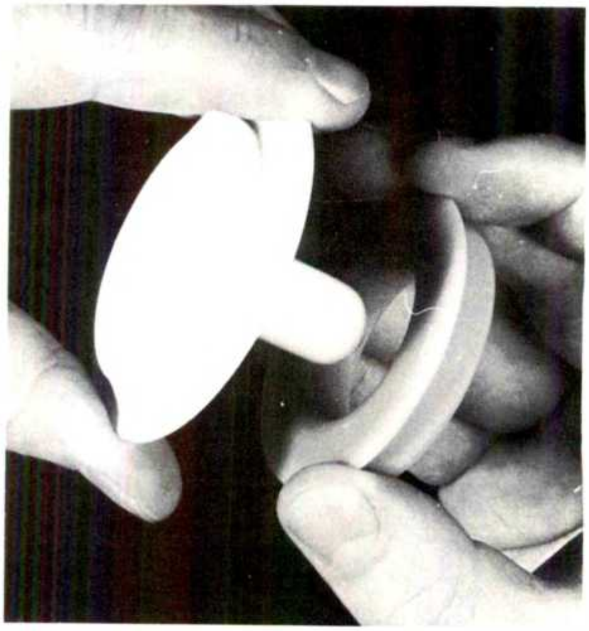

Fig. 1 Magnetic stoma seal. On the right the magnetic ring, coated with *Palacos*, which is to be inserted into the abdominal wall. On the left the magnetic cap with central plug. Both together will render the occluded stoma continent.

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After operation the animals were given streptomycin and penicillin; 3000 ml of balanced intravenous fluids and electrolytes were given daily. On the second post-operative day clear liquids were allowed

Implantation of the Magnetic Ring

This was always done prior to the construction of the conduit.

Group I (12 animals): the ring was implanted as in the patient, *i.e.* subcutaneously after circular skin excision. However, because of the thinner abdominal wall of the dog, the ring had to be placed between the muscles, the edges of which were approximated carefully over the ring with interrupted 2/0 Dexon sutures.

Group II (4 animals). The procedure was undertaken in 2 stages: first by burying the ring transperitoneally through a small midline laparotomy; then, 3 weeks later, the conduit was fashioned. The technique of anchoring the ring was the same as described above.

Technique of the Colonic Conduit

Segments measuring 20 to 25 cm were isolated from the descending colon. Continuity of the intestinal tract was re-established by a standard two-layer-bowel-anastomosis. The proximal end was closed in 2 layers. The distal end was brought out through the previously inserted ring and was fashioned as a stoma on the left abdominal wall (Fig. 2).

Ureterocolic anastomosis was performed according to the technique of Leadbetter and Clarke (1954). After reflux had occasionally been observed, the method was modified by a long-tunnel-technique as proposed by Thompson (1973). The trough in the bowel, measuring 5 to 6 cm in length, was placed close to the site where the bowel enters the abdominal wall, usually in the middle third of the segment. This was done to prevent a "high-insertion-syndrome", which might otherwise be expected with increasing filling and subsequent distension of the colonic segment. All ureters were splinted for 4 days.

After the fourth post-operative week the conduit was occluded daily with the magnetic cap, which was removed every 2 to 3 h to drain the urine. The conduit was left open from 5 p.m. to 8 a.m.

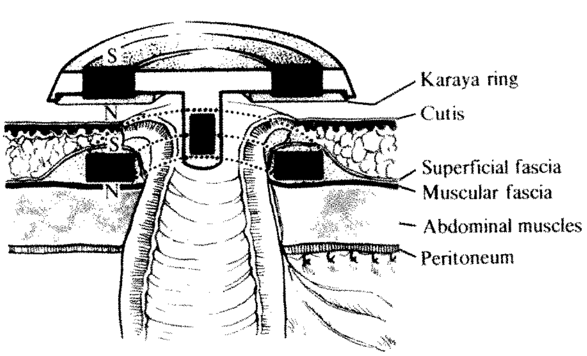

Fig. 2 Cross section through a colostomy occluded with the magnetic stoma seal. Topographical location of the implanted ring between superficial abdominal and muscle fascia.

Table 1

	Total number of animals: 16	
	Group I 12	*Group II* 4
Operative mortality	4	0
Surviving animals	8	4
Infection of magnetic ring	6	0
Animals available for follow-up	2	4

Results

Two dogs died from urinary peritonitis after they had pulled out the splints. Haemorrhage due to venous congestion of the distal colonic stump after division of the inferior mesenteric vein and dehiscence of the bowel anastomosis were other causes of death. The surviving 12 animals (75%) were followed for 3 to 10 months.

In Group I, infection of the ring occurred in 6 of 8 surviving animals with development of a large abscess. The infection occurred as late as 4 weeks after operation. The affected dogs were excluded from the follow-up studies. In Group II, the ring was well accepted by the tissue (Table 1).

Complete continence was achieved in all of the surviving animals. Occasionally, however, some urinary leakage was noted when the reservoir was allowed to become overdistended.

Stomal stenosis was observed in one instance and was related to ischaemia of the distal end of the bowel segment as shown by bluish

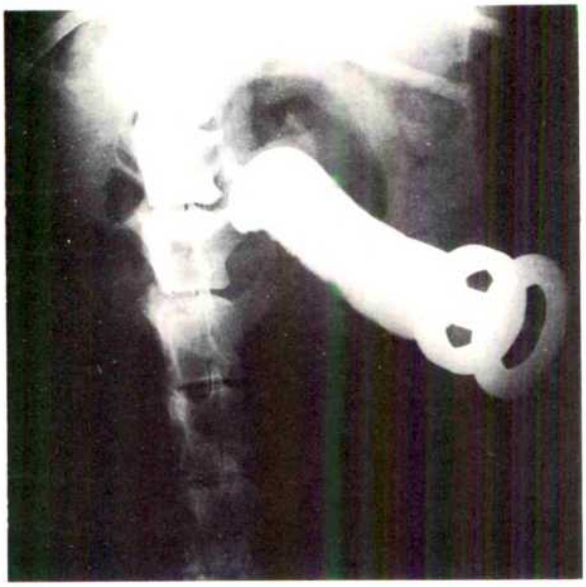

Fig. 3 Dog II-1. The loopogram fails to reveal reflux even under extreme distension of the conduit, applying a pressure of 140 cm of water. Complete continence is provided by the magnetic stoma seal.

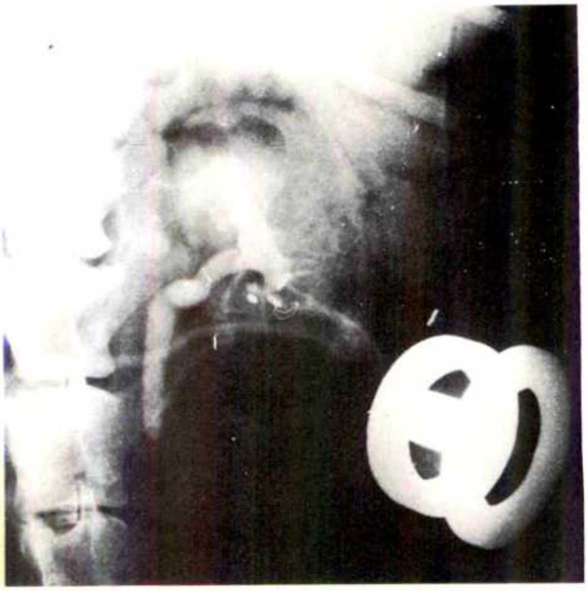

Fig. 4 Dog II-1. Infusion urography. The 15 min film shows no residual urine after the conduit was allowed to empty a moment before exposure. Metal clips mark the end of the conduit. The left ureter is slightly distended proximal to the ureterocolonic anastomosis because of a retroperitoneal kink.

discoloration. This was treated successfully by repeated dilatation, using the central plug of the magnetic cap which acted as a dilator.

The residual urine did not exceed 20 ml (average 5-10 ml). The reservoir capacity ranged from 150 to 250 ml, due to great variation of the colon of the dog. The urine from all conduits was continuously and significantly infected with coliforms, *Proteus* species and *E. coli* predominating.

Renal function was assessed by periodic determination of creatinine and BUN and no deterioration was observed. There were no significant electrolyte changes, including hyperchloraemic acidosis.

The urinary tracts were repeatedly examined by a loopogram (Fig. 3) and infusion urography (Figs. 4, 5). Two ureters, implanted by the Leadbetter-Clarke technique, presented high-pressure-reflux. None of the ureters, implanted by the long-tunnel-technique, revealed any reflux, even when the conduit was extremely distended under a pressure of 140 cm of water.

Discussion

A new magnetic stoma seal has been developed for colostomy and ileostomy patients (Feustel and Hennig, 1975; Feustel *et al.*, 1976). The seal consists of a magnetic ring and a corresponding cap containing a combination of magnets. The magnetic ring is covered by *Palacos*, which is a PMMA plastic material. *Palacos* has been in clinical use for over 20 years and is well tolerated by tissues. The magnets are made from "Samarium-Cobalt", which has a high magnetic energy per unit of volume. The attraction force between ring and cap is improved by adding a central plug to the cap. This results in an almost constant force of 180 to 227 kg, if the distance between ring and cap is >10 mm and <30 mm.

The technique of implantation is simple, and requires anchoring of the ring between superficial abdominal and muscular fascia. Both fascial layers are carefully opposed over the ring with interrupted 2/0 Dexon sutures so that the ring is safely protected by a fascial sheath against the colon, the surface of which is considered to be infected.

Since November 1974 the magnetic seal has been used in 105 colostomy patients; in 41 of these the seal was implanted secondarily. Re-evaluation in April 1976 revealed an infection rate of 20%, necessitating removal of the ring. The results as to continence of the stoma seal were good to satisfactory in 47% and unsatisfac-

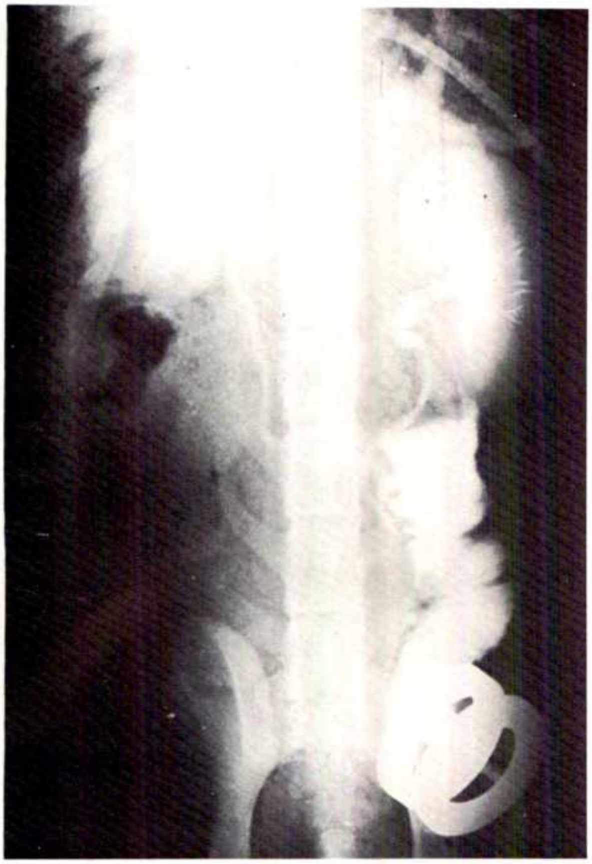

Fig. 5 Dog I-4. Infusion urography. A 15 min film is shown. With the stoma occluded the conduit is well visualised.

tory in 53%. Complete continence can be expected in 70% of the colostomy patients (Hager *et al.*, 1977). Our experimental results compare favourably, because the abdominal wall of the dog meets all criteria necessary for successful implantation of the magnetic ring: smooth, even skin without undue folds, minimal subcutaneous fat and a well built muscular architecture which allows firm anchoring of the ring, eliminating any secondary shifting or tilting of the magnet. On the other hand, secondary ring implantations did not occur in our series, *i.e.* we were not faced with the problems of scarred skin or an improperly placed stoma.

Infection of the ring was the most troublesome complication. Infection occurred either by direct contact with the skin during insertion or by infection spreading from the colonic surface through the created fascial/muscular sheath to the ring. In retrospect, it would appear that our routine skin preparation—mechanical cleansing with ether and ethanol, followed by disinfection with Betadine for 5 min—was not sufficient. The conclusion, that most of our infections were caused by inadequate skin disinfection, is probably correct.

The second route of infection certainly exists, but seems to be less important.

Only vesicostomy and urinary diversions utilising bowel are suitable for conversion into continent reservoirs. We have not yet used the magnetic seal on vesicostomy, since considerable difficulties are still encountered with this procedure (Grimes, 1975). The ileal conduit usually serves as a conduit only, but techniques are being developed to make the stoma continent (Ashken, 1974; Leisinger *et al.*, 1975).

We have used the colonic conduit for our experiments, since the colon offers many advantages (Baker *et al.*, 1963). Two features of the colon need to be particularly emphasised: first, its muscular strength, which ensures efficient voiding, even in the long-term, without undue formation of residual urine, when any distal obstruction or abnormal outflow resistance is eliminated (Turner-Warwick and Ashken, 1967). In cases like ours one may very well assume a low pressure system, since the outflow resistance should approach zero, provided there is no stomal stenosis and this should be prevented by the central plug of the magnetic cap. Also, the colonic wall permits a safe antireflux implantation of the ureters, particularly when a long-tunnel-modification of the Leadbetter-Clarke technique is applied.

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Design of a Urodynamic Questionnaire

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Summary—This paper describes the design of a Urodynamic Questionnaire for female patients. Reference is made to the layout of the clinical history, examination and investigation. Emphasis is placed on the need for clarity and ease of transference of data for computer storage.

The urodynamic questionnaire now in use in the urodynamic unit at St George's Hospital was developed in response to several demands. Firstly to enable questioning of patients to be consistent and without omission. Secondly to collate data for computerisation. Thirdly to eliminate observer bias, enabling different doctors to use the questionnaire in the clinic. Fourthly the questionnaire makes a very legible form of note-taking and is easily comprehensible to doctors in other specialities. Finally it is a fast and efficient method of dealing with a large patient throughput in the clinic.

In the preparation of the questionnaire other such documents were consulted. The Middlesex Hospital and Institute of Urology Questionnaires both ask similar questions, the former recording the history and results of investigations and the latter the history and clinical examination. The Incontinence Clinic Questionnaire produced by the University Hospital of South Manchester is detailed and includes many general features as well as special questions related to voiding disorders. The "Incontinence Checklist" by Hodgkinson (1963) is searching in its questions but is self-administered and therefore only concerned with the history. None of these questionnaires allows for the computerisation of data; this is a feature of the urological questionnaire produced by the Department of Urology at St Bartholomew's Hospital, which records all patient data on magnetic tape (Wickham *et al.*, 1975). The University of Bristol Bladder Function Study is comprehensive in its questioning and also permits the computerisation of history, examination and initial investigations, although follow-up information is not included.

The style and layout of the questionnaire were worked out in conjunction with the Department of Clinical Epidemiology and Social Medicine, who suggested the design with numerical coding on the questionnaire. The numbers could then be transferred on to punch cards for later storage on magnetic tape.

The questionnaire consists of 3 differently coloured sheets printed on 2 copies of NCR (self-carbonating) paper for use during the initial consultation and primary investigations, and a fourth double sheet printed on ordinary paper which is used for follow-up. One copy is filed in the patient's case notes and the other is retained in the unit.

The patient's identification label, unit number and date of initial consultation are recorded at the top of every page. The left-hand side of each sheet is devoted to questions and their answers, the answers being indicated by a minimum number of words or by ringing a number. On the right-hand side of each sheet there are boxes corresponding to the appropriate questions, which are used for coding the responses for transference on to punch cards.

The first data sheet (Fig. 1) is concerned only with the present history. First the patient's main complaints are recorded in her own words. This is followed by a urological checklist, which in addition to asking about stress incontinence, frequency and urgency, includes questions about voiding difficulties and retention of urine. In addition certain gynaecological symptoms are recorded, including prolapse and dyspareunia. The patient is asked about her menstrual pattern and its effect on her urological symptoms, and whether she takes the oral contraceptive pill. Special mention is made of neurological symptoms related to S_2, S_3 and S_4 outflow such as rectal soiling and weakness of the legs, and the

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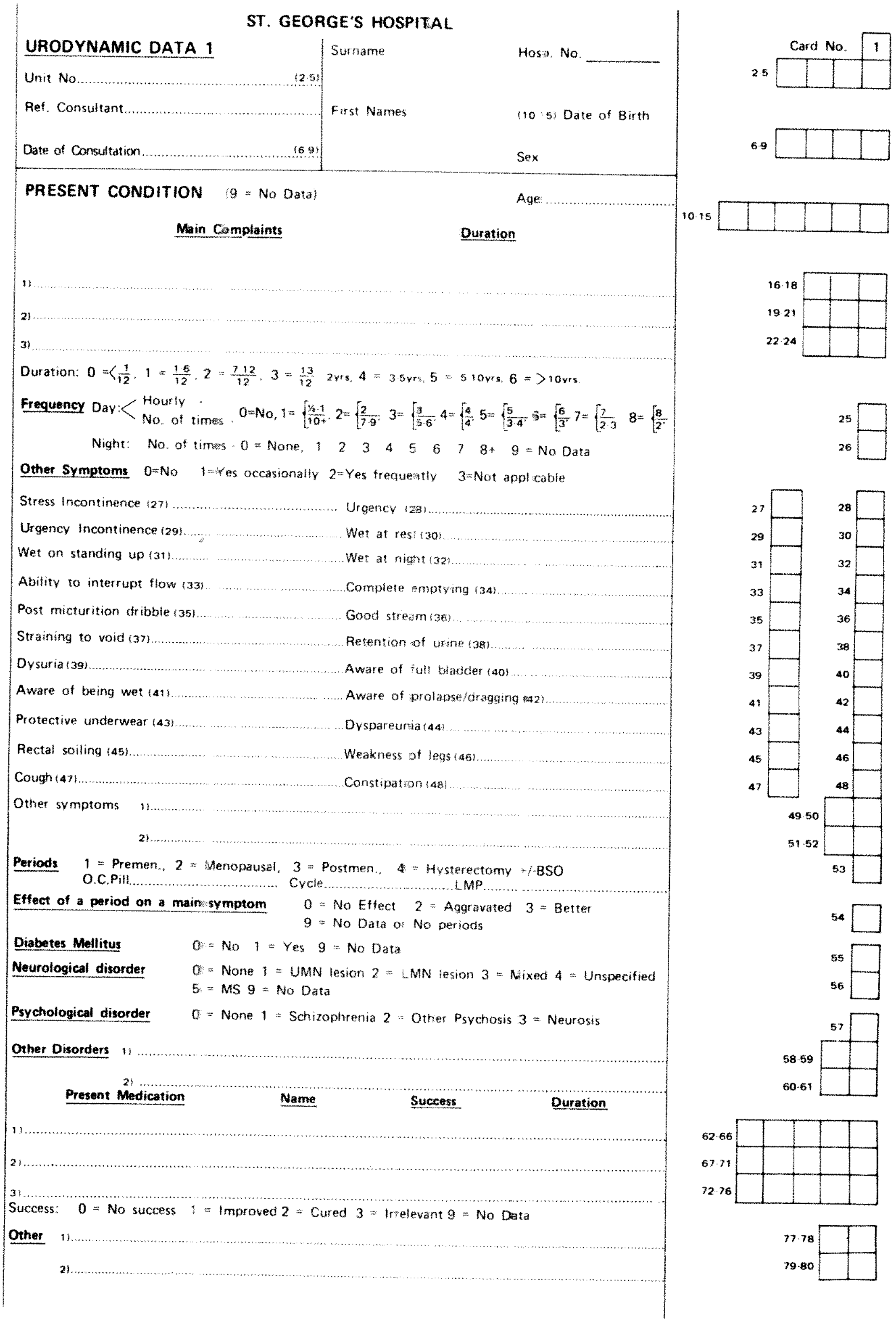


ST. GEORGE'S HOSPITAL

URODYNAMIC DATA 1

Unit No...(2-5)

Ref. Consultant...

Date of Consultation...(6-9)

Surname

First Names

Hosp. No. ________

(10-15) Date of Birth

Sex

Card No. 1

2-5

6-9

10-15

PRESENT CONDITION (9 = No Data)

Age.................................

Main Complaints **Duration**

1)...

2)...

3)...

16-18

19-21

22-24

Duration: 0 =$<\frac{1}{12}$, 1 = $\frac{1\text{-}6}{12}$, 2 = $\frac{7\text{-}12}{12}$, 3 = $\frac{13}{12}$ 2yrs, 4 = 3-5yrs, 5 = 5-10yrs, 6 = >10yrs.

Frequency Day: Hourly · No. of times · 0=No, 1= $\begin{cases}\frac{1}{2}\text{-}1\\10+\end{cases}$, 2= $\begin{cases}2\\7\text{-}9\end{cases}$, 3= $\begin{cases}3\\5\text{-}6\end{cases}$, 4= $\begin{cases}4\\4\end{cases}$, 5= $\begin{cases}5\\3\text{-}4\end{cases}$, 6= $\begin{cases}6\\3\end{cases}$, 7= $\begin{cases}7\\2\text{-}3\end{cases}$, 8= $\begin{cases}8\\2\end{cases}$

Night: No. of times · 0 = None, 1 2 3 4 5 6 7 8+ 9 = No Data

25

26

Other Symptoms 0=No 1=Yes occasionally 2=Yes frequently 3=Not applicable

Stress Incontinence (27)................ Urgency (28)................

Urgency Incontinence (29)................ Wet at rest (30)................

Wet on standing up (31)................ Wet at night (32)................

Ability to interrupt flow (33)................ Complete emptying (34)................

Post micturition dribble (35)................ Good stream (36)................

Straining to void (37)................ Retention of urine (38)................

Dysuria (39)................ Aware of full bladder (40)................

Aware of being wet (41)................ Aware of prolapse/dragging (42)................

Protective underwear (43)................ Dyspareunia (44)................

Rectal soiling (45)................ Weakness of legs (46)................

Cough (47)................ Constipation (48)................

Other symptoms 1)................

2)................

27 28

29 30

31 32

33 34

35 36

37 38

39 40

41 42

43 44

45 46

47 48

49-50

51-52

53

Periods 1 = Premen., 2 = Menopausal, 3 = Postmen., 4 = Hysterectomy +/-BSO
O.C.Pill................ Cycle................ LMP................

Effect of a period on a main symptom 0 = No Effect 2 = Aggravated 3 = Better
9 = No Data or No periods

54

Diabetes Mellitus 0 = No 1 = Yes 9 = No Data

Neurological disorder 0 = None 1 = UMN lesion 2 = LMN lesion 3 = Mixed 4 = Unspecified
5 = MS 9 = No Data

55

56

Psychological disorder 0 = None 1 = Schizophrenia 2 = Other Psychosis 3 = Neurosis

57

Other Disorders 1)................

2)................

58-59

60-61

Present Medication **Name** **Success** **Duration**

1)................

2)................

3)................

62-66

67-71

72-76

Success: 0 = No success 1 = Improved 2 = Cured 3 = Irrelevant 9 = No Data

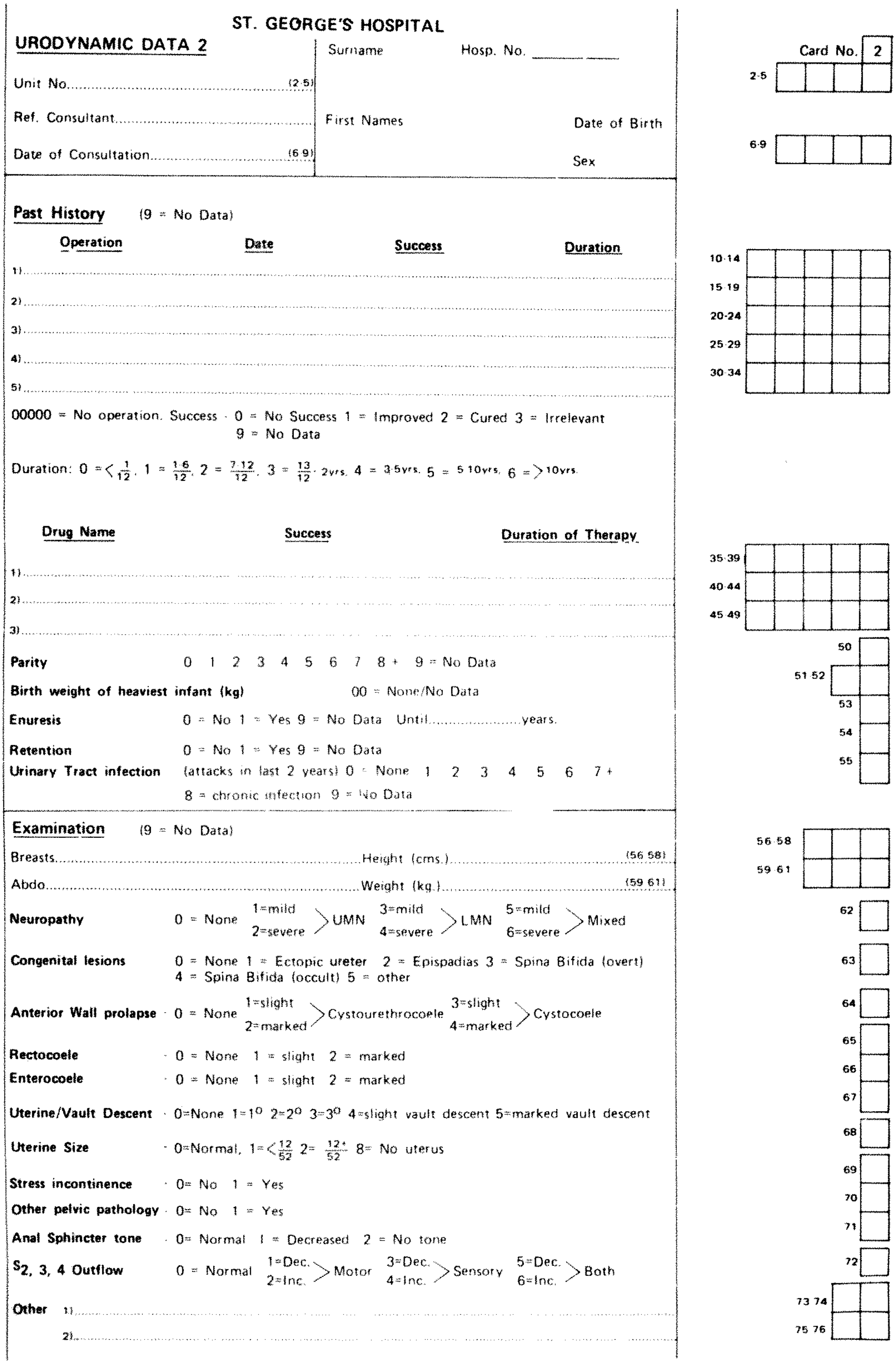
Other 1)................

2)................

77-78

79-80

Fig. 1



ST. GEORGE'S HOSPITAL

URODYNAMIC DATA 2

Card No. 2

Unit No. .... (2 5) — 2-5

Ref. Consultant ....

Date of Consultation .... (6 9) — 6-9

Surname

Hosp. No. ________

First Names

Date of Birth

Sex

Past History (9 = No Data)

Operation	**Date**	**Success**	**Duration**
1)			
2)			
3)			
4)			
5)			

10-14, 15-19, 20-24, 25-29, 30-34

00000 = No operation. Success · 0 = No Success 1 = Improved 2 = Cured 3 = Irrelevant 9 = No Data

Duration: 0 = $<\frac{1}{12}$, 1 = $\frac{1\text{-}6}{12}$, 2 = $\frac{7\text{-}12}{12}$, 3 = $\frac{13}{12}$-2yrs, 4 = 3-5yrs, 5 = 5-10yrs, 6 = $>$10yrs.

Drug Name	**Success**	**Duration of Therapy**
1)		
2)		
3)		

35-39, 40-44, 45-49

Parity 0 1 2 3 4 5 6 7 8+ 9 = No Data — 50

Birth weight of heaviest infant (kg) 00 = None/No Data — 51 52

Enuresis 0 = No 1 = Yes 9 = No Data Until............years. — 53

Retention 0 = No 1 = Yes 9 = No Data — 54

Urinary Tract infection (attacks in last 2 years) 0 = None 1 2 3 4 5 6 7+ 8 = chronic infection 9 = No Data — 55

Examination (9 = No Data)

Breasts............ Height (cms.)............ (56 58) — 56 58

Abdo............ Weight (kg.)............ (59 61) — 59 61

Neuropathy 0 = None 1=mild 2=severe > UMN 3=mild 4=severe > LMN 5=mild 6=severe > Mixed — 62

Congenital lesions 0 = None 1 = Ectopic ureter 2 = Epispadias 3 = Spina Bifida (overt) 4 = Spina Bifida (occult) 5 = other — 63

Anterior Wall prolapse · 0 = None 1=slight 2=marked > Cystourethrocoele 3=slight 4=marked > Cystocoele — 64

Rectocoele · 0 = None 1 = slight 2 = marked — 65

Enterocoele · 0 = None 1 = slight 2 = marked — 66

Uterine/Vault Descent · 0=None 1=1° 2=2° 3=3° 4=slight vault descent 5=marked vault descent — 67

Uterine Size · 0=Normal, 1=$<\frac{12}{52}$ 2= $\frac{12+}{52}$ 8= No uterus — 68

Stress incontinence · 0= No 1 = Yes — 69

Other pelvic pathology · 0= No 1 = Yes — 70

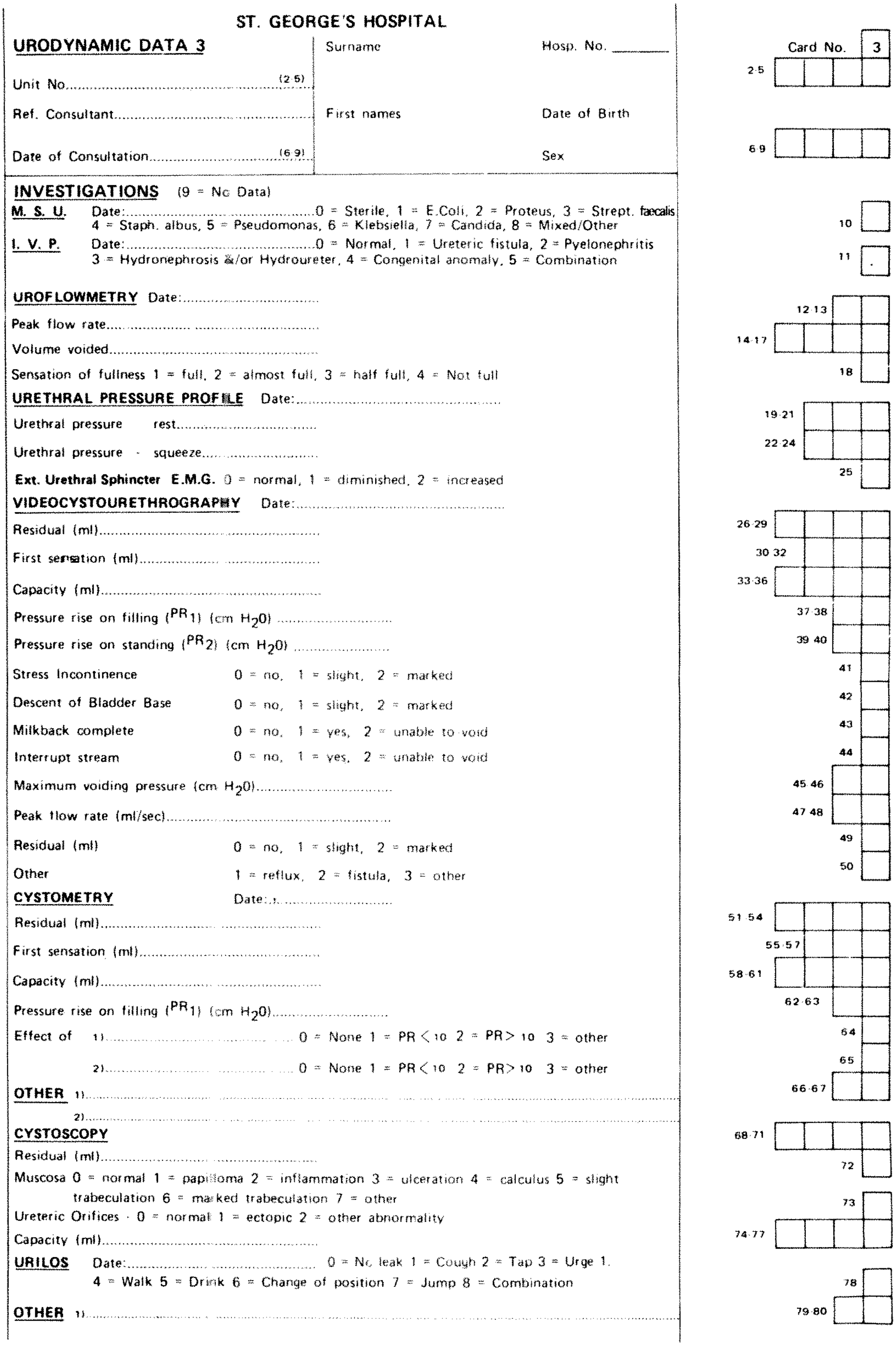
Anal Sphincter tone · 0= Normal 1 = Decreased 2 = No tone — 71

S_2, 3, 4 Outflow 0 = Normal 1=Dec. 2=Inc. > Motor 3=Dec. 4=Inc. > Sensory 5=Dec. 6=Inc. > Both — 72

Other 1) .... — 73 74

2) .... — 75 76

Fig. 2



ST. GEORGE'S HOSPITAL

URODYNAMIC DATA 3

Surname Hosp. No. ________

Unit No...(2-5)

Ref. Consultant...

First names Date of Birth

Date of Consultation.......................................(6-9)

Sex

INVESTIGATIONS (9 = No Data)

M. S. U. Date:..0 = Sterile, 1 = E.Coli, 2 = Proteus, 3 = Strept. faecalis 4 = Staph. albus, 5 = Pseudomonas, 6 = Klebsiella, 7 = Candida, 8 = Mixed/Other

I. V. P. Date:..0 = Normal, 1 = Ureteric fistula, 2 = Pyelonephritis 3 = Hydronephrosis &/or Hydroureter, 4 = Congenital anomaly, 5 = Combination

UROFLOWMETRY Date:...................................

Peak flow rate...

Volume voided...

Sensation of fullness 1 = full, 2 = almost full, 3 = half full, 4 = Not full

URETHRAL PRESSURE PROFILE Date:...

Urethral pressure rest...................................

Urethral pressure - squeeze...........................

Ext. Urethral Sphincter E.M.G. 0 = normal, 1 = diminished, 2 = increased

VIDEOCYSTOURETHROGRAPHY Date:...

Residual (ml)...

First sensation (ml)..

Capacity (ml)..

Pressure rise on filling ($^{PR}1$) (cm H_2O) ....

Pressure rise on standing ($^{PR}2$) (cm H_2O) ....

Stress Incontinence 0 = no, 1 = slight, 2 = marked

Descent of Bladder Base 0 = no, 1 = slight, 2 = marked

Milkback complete 0 = no, 1 = yes, 2 = unable to void

Interrupt stream 0 = no, 1 = yes, 2 = unable to void

Maximum voiding pressure (cm H_2O)..................................

Peak flow rate (ml/sec)..

Residual (ml) 0 = no, 1 = slight, 2 = marked

Other 1 = reflux, 2 = fistula, 3 = other

CYSTOMETRY Date:...............................

Residual (ml)..

First sensation (ml)..

Capacity (ml)..

Pressure rise on filling ($^{PR}1$) (cm H_2O)..............................

Effect of 1)..0 = None 1 = PR < 10 2 = PR > 10 3 = other

2)..0 = None 1 = PR < 10 2 = PR > 10 3 = other

OTHER 1)..

2)..

CYSTOSCOPY

Residual (ml)..

Muscosa 0 = normal 1 = papilloma 2 = inflammation 3 = ulceration 4 = calculus 5 = slight trabeculation 6 = marked trabeculation 7 = other

Ureteric Orifices - 0 = normal 1 = ectopic 2 = other abnormality

Capacity (ml)..

URILOS Date:.. 0 = No leak 1 = Cough 2 = Tap 3 = Urge 1. 4 = Walk 5 = Drink 6 = Change of position 7 = Jump 8 = Combination

OTHER 1)..

Card No. 3

2-5
6-9
10
11
12-13
14-17
18
19-21
22-24
25
26-29
30-32
33-36
37-38
39-40
41
42
43
44
45-46
47-48
49
50
51-54
55-57
58-61
62-63
64
65
66-67
68-71
72
73
74-77
78
79-80

Fig. 3

RODYNAMIC DATA IV ST. GEORGE'S HOSPITAL

	FOLLOW-UP VISITS	Date:	Date:	Date:	Date:
HISTORY	General Health				
	Main complaint				
	Other complaints				
	Wet or Dry				
	Frequency $^{D}/_{N}$				
	Stress Incontinence				
	Urgency				
	Urgency Incontinence				
	Complete emptying				
	Good stream				
	Straining to void				
	Retention of urine				
	Sensation of Prolapse/Dragging				
	Other Symptoms 1.				
	2.				
EXAMINATION	Weight (kgm)				
	General conditions				
	Anterior wall prolapse				
	Posterior wall prolapse				
	Uterine/Vault descent				
	Stress Incontinence				
	Pelvic pathology				
	Other signs 1.				
	2.				
INVESTIGATIONS	M. S. U.				
	Uroflowmetry				
	Urilos				
	V. C. U.				
	Cystometry				
	Cystoscopy				
	Other investigations 1.				
	2.				
TREATMENT	Surgery				
	Drug therapy				
	Biofeedback				
	Devices				
	Catheter				
	Referred to another consultant				
	Other therapy 1.				
	2.				
	Next Appointment				

Fig. 4

patient is asked about any known neurological disorders. Other medical conditions are recorded with special emphasis on psychiatric disorders. Finally a drug history is taken and note is made of tricyclic antidepressant, beta adrenergic stimulator, anticholinergic or hormonal therapy.

The second sheet (Fig. 2) is divided into 2 parts; the first half is devoted to the patient's past history and the rest to the clinical examination. Previous pelvic surgery is recorded with dates and, if it was performed in connection with the present complaint, its success or otherwise is noted. Previous urinary symptoms such as enuresis and urinary tract infection are recorded. An obstetrical history is taken and note is made of the birth weight of the heaviest infant.

As part of the routine clinical examination the patient is weighed and measured. General examination includes the breasts and abdomen. The gynaecological features are recorded in detail and include all forms of gynaecological prolapse as well as testing for stress incontinence. A neurological examination is carried out with particular emphasis on the sensory and motor aspects of S_2, S_3 and S_4 outflow.

The third sheet (Fig. 3) is concerned with urodynamic investigations. These include midstream specimen of urine, cystoscopy, uroflowmetry and videocystourethrography or cystometry, which are performed routinely. In addition space is available for the results of Urilos Nappy Test, urethral pressure profile, external urethral sphincter EMG and intravenous pyelography.

The fourth sheet (Fig. 4) is folded over in the patient's notes and enables the data from 6 follow-up visits to be recorded in a brief form. The same urodynamic symptoms are noted and more detailed information can be written on the reverse side of this sheet, where space is available for the final diagnosis to be recorded and treatment changes to be written down. It is not practical to use NCR paper for this data sheet (as it is used on several occasions), so it is printed on ordinary paper and 2 identical copies are kept. When the first 3 sheets have been completed the responses are coded and details recorded on punch cards, 1 punch card being made out for each data sheet. The second copies of the questionnaire are then torn off and stored in the urodynamic unit. The diagnosis, treatment and progress are coded, a new punch card being made out for each follow-up visit.

The questionnaire is now in regular use in the urodynamic clinic and has been tried on over 400 patients. It reduces the time spent writing notes in the clinic and makes all the information easily legible. It ensures that the questions are asked in the same form on each occasion, thus providing a consistent data bank of easily accessible information.

Acknowledgements

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Carcinoma of the Penis

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Summary—Sixty-three patients with squamous cell carcinoma of the penis have been reviewed. The 3 year survival was 77%, and the 5 year survival was 59%.

Prognosis was related to both clinical staging and histological grading. Stage I and II carcinomas were best treated by surgery alone. Stage III and IV carcinomas were best treated by local amputation of the penis combined with radiotherapy to the inguinal nodes.

Surgery as a primary treatment for clinically positive nodes was successful in less than half the cases treated, and in this series was always followed by wound infection and lymphoedema.

Tender, enlarged inguinal lymph nodes should be observed for up to 3 months following primary treatment, as a large percentage of these nodes are inflammatory and subside spontaneously.

Carcinoma of the penis is an uncommon lesion and both general and urological surgeons may be undecided as to the best form of treatment. Primary surgery has been advocated by some authors including Lesser and Schwarz (1955), Staubitz *et al.* (1955), Savage (1957) and Marcial *et al.* (1962). Others have advised radiotherapy as the initial treatment (Engelstad, 1948; Murrell and Williams, 1965). Finally, a combination of surgery and radiotherapy has been described by Lederman (1953), Cox (1954) and Ekström and Edsmyr (1958).

In view of these different opinions a retrospective review of 63 cases of carcinoma of the penis presenting in the Department of Surgery and Urology at the Bristol* and Bath United Hospitals over the period 1962-76 was carried out to try and determine which method of treatment to advise any future patients presenting with this lesion.

Patients and Methods

During the 15 year period under review a total of 73 patients with lesions of the penis was considered. Of these, 10 cases were not considered acceptable and were excluded (Table 1). The remaining 63 patients had primary squamous cell carcinoma of the penis.

The age at presentation varied from 32 to 93 years with a mean age of 58 years. Thirty-two patients presented with a painful ulceration, a purulent or blood stained discharge and a non-retractile foreskin. Fifteen patients had swelling and inflammation with a non-retractile foreskin. Sixteen patients presented with a nodule on the glans penis. The duration of these features before presentation in hospital was from 3 weeks to 3 years with a mean duration of 21 weeks. Fifty-nine patients were married and in the 55 patients where relevant information was available 51 were fertile. There was no change in the overall incidence of carcinoma of the penis during this 15 year period. The patients had a wide range of occupations, but in none was this significant in relation to aetiology. One patient had an

Table 1 Pathological Diagnosis in 73 Tumours of the Penis

Primary squamous cell carcinoma of penis	63
Benign lesions	4
Primary malignant melanoma of penis	2
Transitional cell carcinoma of penis (arising from urothelium)	2
Primary reticulum cell sarcoma of penis	1
Carcinoma *in situ*	1
Total	73

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* Bristol Royal Infirmary, Southmead Hospital and Frenchay Hospital.

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epispadias and in the remainder none had been circumcised before puberty. In the 53 cases where the information was available, 24 men had evidence of previous urinary infection. Seven patients had a history of venereal disease. In 11 patients leukoplakia had been found prior to the development of the carcinoma.

The tumours were each staged according to the classification described by Jackson (1966) (Table 2). The histological grading of the tumour is shown in Table 3.

Treatment

In view of the length of the period of this retrospective review and the fact that these patients were treated by many surgical teams, it was not surprising that different methods of treatment of carcinoma of the penis had been employed (Table 4). Radiotherapy alone was used in 5 patients with Stage I carcinoma of the penis. The dose was 6000 rads to the penis only, given over a 6 week period. Those patients with Stage II carcinoma who received radiotherapy did so at varying intervals following initial amputation either prophylactically* (5 patients) or as a result of recurrence proven histologically (6 patients). The radiotherapy was given to the groins only, in the dose of up to 6000 rads over a 6 week period.

When radiotherapy was used in Stage III and IV carcinoma it was given after the amputation wound had healed in a dose of up to 6000 rads to groins or groins and penis (3 cases) over a 6 week period. Histological proof of inguinal node metastases was obtained in each case.

Table 2 Staging of Carcinoma of Penis

		No. of patients
Stage I	Tumour confined to glans or prepuce	17
Stage II	Tumour extending into the urethra or beyond the corona	26
Stage III	Inguinal node involvement but nodes still mobile	16
Stage IV	Fixed involved inguinal nodes, direct extension of distant metastases	4

Table 3 Histological Grading

Degree of differentiation	*No. of patients*
Well differentiated	33
Moderately differentiated	22
Poorly differentiated	7
Anaplastic	1
Total	63

Results

The overall results of this wide range of different treatments were encouraging. Forty-six of the 59 patients were alive at 3 years (77%) and 32 out of 54 at 5 years (59%). The mortality figures include 10 patients dying from causes, mainly cardiovascular, unrelated to the original tumour. Thus the corrected 5 year survival rate was 77%. The results of the different treatments have been analysed in relation to the clinical staging of the tumour and divided into 2 groups.

1. Stage I and II Tumours (Tables 5 and 6)

Forty-three of the 63 patients (68%) in this series were Stage I and II, that is, tumour confined to the penis. Twenty-six of these patients were treated by either local excision or partial amputation and 1 patient by cryosurgery. Seventeen of these patients were alive and well at 5 years, 2 at 4 years and 2 at 2 years. Five of the 9 patients who had surgery followed by radiotherapy were alive and well at 5 years and 2 at between 3 and 4 years. The 8 patients who died in these groups did so as a result of intercurrent disease (*e.g.* myocardial infarct, bronchopneumonia), with none dying as a result of carcinoma of the penis. Their age range was 52 years to 94 years, with a mean age of 80 years. Of the 5 patients who had

Table 4 Methods of Treatment

	No. of patients
Local excision	1
Partial amputation	25
Partial amputation and radiotherapy	18
Partial amputation and radiotherapy and block dissection	3
Radiotherapy alone	5
Cryosurgery alone	1
Total amputation and radiotherapy	9
Total amputation and block dissection	1

---

* Although it has not been the policy of this centre, 5 patients had prophylactic radiation in this group.

Table 5 Stage I Tumours

Treatment used	*No. of patients*	*Degree of differentiation*			*Died of carcinoma*	*Died of intercurrent disease*	*No. of patients surviving*	*5 year survival*
		Well	*Moderate*	*Poorly*				
Local excision	1	1	–	–	0	–	1	1
Partial amputation*	10	10	–	–	0	3	7	6
Cryosurgery	1	1	–	–	0	–	1	1
Radiotherapy to penis alone †	5	3	2	–	1	1	3	2

* One patient follow-up 4 years.
† One patient follow-up 2 years..

radiotherapy alone, 2 were alive and well at 5 years, 1 was alive and well at 2 years, but 1 patient died from carcinomatosis 3 years after treatment and another died from intercurrent disease. Two patients who had undergone partial amputation of penis followed by radiotherapy subsequently developed positive inguinal lymph nodes 6 and 8 months later and then underwent block dissection. One of these patients developed gross lymphoedema but is alive and well at 6 years. The other died at 18 months as the result of disseminated carcinoma of the penis. This latter patient was the only one in Stage I and Stage II with a poorly differentiated tumour, the rest having a well or moderately well differentiated lesion.

2. *Stage III and IV Tumours* (Tables 7 and 8)

Sixteen patients in this series had Stage III carcinoma of the penis and 6 had died as a result of their carcinoma within 5 years, 1 patient was killed in a road traffic accident at 2 years, 7 patients were alive and well at 5 years, 1 patient at 4 years and 1 at 1 year. Nine patients had a partial amputation followed by radiotherapy and 5 patients had a total amputation followed by radiotherapy. One patient had a partial amputation and radiotherapy followed by block dissection, and the last patient had a total amputation with block dissection. Both patients who had a block dissection developed lymphoedema. Five of the 6 patients in this group who died had had a total amputation and radiotherapy, and the sixth patient had had a total amputation with a block dissection. Five of the 6 patients who died had either poorly differentiated or anaplastic tumours.

The 4 patients with Stage IV disease were treated by total amputation and radiotherapy. All were dead within 3 years:

Table 6 Stage II Tumours

Treatment used	*No. of patients*	*Degree of differentiation*			*Died of carcinoma*	*Died of intercurrent disease*	*No. of patients surviving*	*5 year survival*
		Well	*Moderate*	*Poorly*				
Partial amputation*	15	8	7	–	–	3	12	9
Partial amputation followed by radiotherapy to groin †	9	2	7	–	–	2	7	5
Partial amputation followed by radiotherapy to groin and later block dissection	2	–	1	1	1	–	1	1

* Three patients—follow-up between 2 years and 4 years.
† Two patients—follow-up between 3 years and 4 years.

Table 7 Stage III Tumours

Treatment used	*No. of patients*	*Degree of differentiation*				*Died of carcinoma*	*Died of inter-current disease*	*No. of patients surviving*	*5 year survival*
		Well	*Moderate*	*Poorly*	*Anaplastic*				
Partial amputation and radiotherapy*	9	7	2	–	–	0	1	8	6
Partial amputation and radiotherapy and block dissection	1	1	–	–	–	0	0	1	1
Total amputation and block dissection	1	–	1	–	–	1	0	0	0
Total amputation and radiotherapy	5	–	–	4	1	5	0	0	0

* Two patients—follow-up 1 year and 4 years.

Table 8 Stage IV Tumours

Treatment used	*No. of patients*	*Degree of differentiation*				*Died of carcinoma*	*Died of intercurrent disease*	*No. of patients surviving 5 years*
		Well	*Moderate*	*Poorly*	*Anaplastic*			
Total amputation and radiotherapy	4	–	2	2	–	4	–	0 (0%)

Discussion

The results in this series showed a 77% 3 year and a 59% 5 year survival and compare favourably with other published results. Cox (1954), using radium for the penis and a block dissection for clinically positive nodes, had a 37% 5 year survival in 60 patients. Lesser and Schwarz (1955), using surgery, had a 48.6% 5 year survival in 35 cases. Slightly better results were obtained by Lederman (1953) who used radiotherapy combined with surgery. His 5 year survival was 50.8% in 183 patients. Murrell and Williams (1965), using radiotherapy, had a 3 year survival of 50.2% and a 5 year survival of 40.4% in 108 patients. Marcial *et al.* (1962), using surgery had a 5 year survival rate of 50.8% in 183 patients. Frew *et al.* (1967) had a 53% 5 year survival in 46 patients with carcinoma of the penis treated by surgery. The best recorded results in the literature are those of Engelstad (1948) who, using radium for the penis and groins with surgery later for uncontrolled disease, had a 3 year survival of 70.8% in 72 patients and a 5 year survival of 66.7% in 57 patients. Ekström and Edsmyr (1958), using surgery to the penis and clinically positive nodes and telegamma irradiation to clinically negative nodes, had a 5 year survival of 69% in 177 patients.

The 5 year survival rate for Stage I and II tumours in this series was 70%. This compares with Beggs and Spratt (1964), where the treatment was primarily surgical, who had a 72.5% 5 year survival in 57 patients. Murrell and Williams (1965) reported a 52% 5 year survival in patients with Stage I and II carcinoma of the penis treated by radiotherapy. Engelstad (1948) treated the penis by teleradium and radium mould, giving 3500-3700 rads in 3 days, and had a 5 year survival of 66%. In both series surgery was necessary for persistent or recurrent cases.

Thus it would seem that radiotherapy alone does not control the primary carcinoma as effectively as surgery, and in particular radiotherapy is not likely to be effective in controlling the primary lesion where the tumour is either septic or invading the corpora or urethra. Furthermore, the advantage of the short hospital stay associated with surgical amputation compares favourably with 6 weeks radiotherapy treatment followed by 6-8 weeks discomfort due to the local tissue reaction. This is an important consideration, as many patients are elderly and infirm.

One further fact of interest appeared from this study. The policy of deferring a decision on the treatment of inguinal lymph nodes until the primary lesion has been treated and the wound healed did not lead to any case passing from operable to inoperable stage. In 24 patients there were enlarged, tender, palpable inguinal nodes which resolved completely after surgery to the penile lesion. This confirms the findings of Cox (1954) and Beggs and Spratt (1964) that early prophylactic groin dissection led to a high percentage of unnecessary groin dissections and of Harlin (1952) who found careful observation of the groins was necessary to allow infection to subside. Provided that the nodes are not increasing in size or fixity one should be prepared to observe the patients at regular intervals. In the 4 patients where block dissection was performed, tumour deposits were present in 3 cases, of whom 2 died and 1 is still alive and well at 6 years. In the remaining patient where the nodes were negative, lymphoedema occurred subsequently, but the patient is still alive at 11 years.

Acknowledgement

We would like to thank our other urological and general surgical colleagues in Bristol and Bath for permission to review their patients. We are indebted to Miss Michelle Dent for typing this manuscript.

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Case Reports

Metastasis from Renal Carcinoma to a Phalanx of the Hand

Metastases from renal carcinoma are rarely found in the hand (Kerin, 1958; Ruggero and Bori, 1955). Uriburu *et al.* (1976) in a recent review of the literature for tumours metastatic to the hand, found 90 cases and from these only 4 were of renal origin.

Case Report

A 48-year-old female underwent a hysterectomy in August 1974 for a squamous cell carcinoma of the uterine cervix. She was treated post-operatively with radiation therapy and was discharged in good condition. In August 1975 she presented with gross haematuria. IVP showed a renal tumour and nephrectomy was performed. The histology showed clear cell carcinoma. In January 1976 she complained of swelling in the distal segment of the left ring finger with progressive pain and local redness. X-rays showed an osteolytic lesion of that phalanx (Fig. 1). Accordingly, a radical amputation was carried out. Histology showed a secondary clear cell tumour consistent with the renal primary (Fig. 2). The patient died 2 months later of disseminated disease.

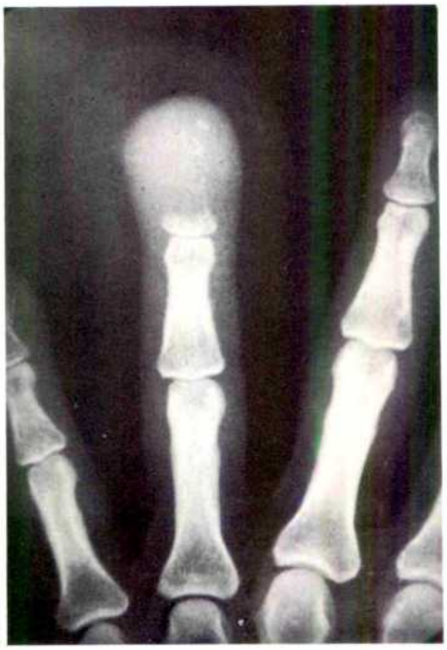

Fig. 1

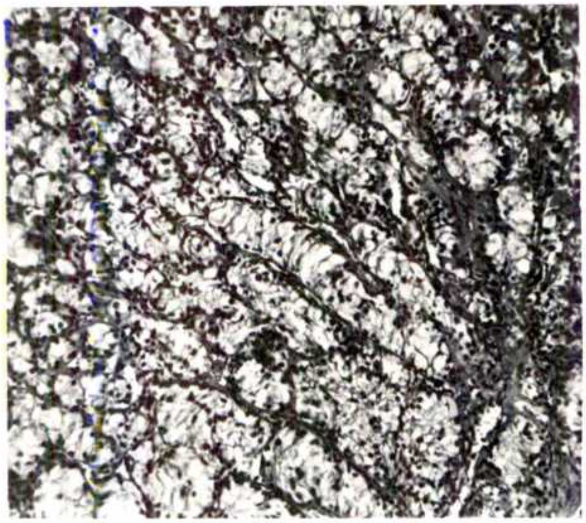

Fig. 2

Comment

The presentation resembles an infectious condition, as in the case of our patient, and in most reported cases the condition is confused with a felon, osteomyelitis or even tuberculosis (Kerin, 1958). The presence of such a secondary from a renal carcinoma is usually indicative of generalised metastatic disease.

Acknowledgement

I would like to thank Dr José Ribeiro Menezes Netto from Santo Antonio Hospital for the histological diagnosis.

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Successful Pregnancy in a Patient with Previous Ectopia Vesicae

Exstrophy of the bladder occurs in 1 in every 40,000 births of the general population, and the incidence of recurrence in a family with a previous child with exstrophy is 1 in 200 (Ezell and Carlson, 1970).

Case Report

The patient, a 19-year-old gravida 2 para 0 was born with an ectopic bladder which was dealt with in infancy; the procedures included a double ureterostomy and bilateral sacro-iliac osteotomy in order to close the front of the pelvis. At the age of 9 years the left kidney had shown deterioration and the ureterostomy stump was revised and subsequently converted to an ileal loop diversion. Renal function subsequently remained satisfactory, though there was mild bilateral hydronephrosis.

The ante-natal period was uneventful apart from a persistent breech presentation (Fig.). Renal function remained normal and urine culture negative. Labour was induced at 41 weeks gestation by artificial rupture of the forewaters. It was noted that the cervix was almost flush with the perineum. An uneventful 6 h labour ensued and an assisted breech delivery was performed, a healthy male infant of 2320 g being delivered. The anterior abdominal wall was under some tension during pregnancy and delivery and this was relieved at the latter stage by a right medio-lateral episiotomy. The post-natal course was normal except for a coliform urinary tract infection.

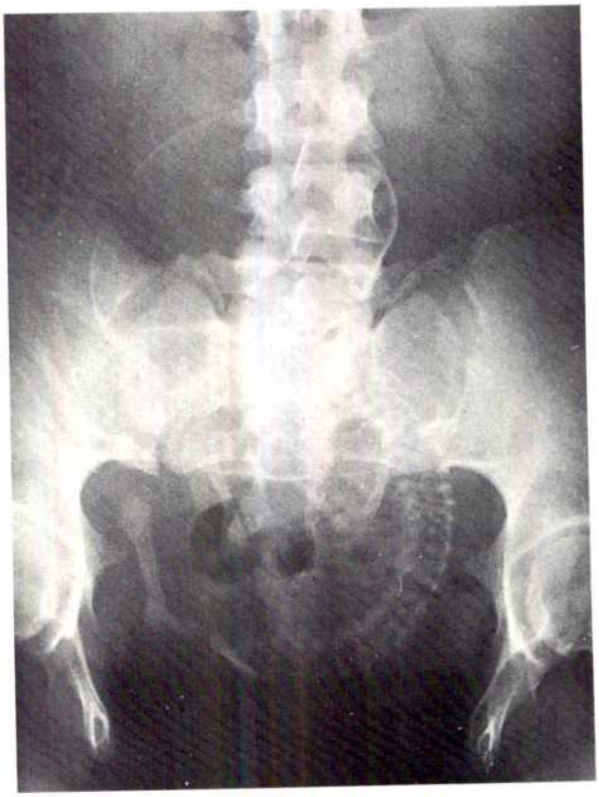

Fig.

Comment

The ileal diversion in this case caused no antenatal problems, whereas cases with ureterosigmoidostomy may suffer exacerbation of hyperchloremic acidosis, uremia and anaemia (Killam *et al.*, 1967). Vaginal delivery may aggravate an underlying tendency to genital prolapse (Stanton, 1974). However, cephalopelvic disproportion is less likely and the straightforward labour and delivery in the case described support this contention.

Acknowledgements

We would like to thank Mr D. F. Ellison Nash, St Bartholomew's Hospital, London and Mr P. J. Dwyer, Kent and Canterbury Hospital for their help in the preparation of this case report.

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Killam, A., Grillo, D. and Summerson, D. J. (1967). Pregnancy and delivery after ureterosigmoidostomy. *American Journal of Obstetrics and Gynecology*, **97**, 278-279.

Stanton, S. L. (1974). Gynecologic complications of epispadias and bladder exstrophy. *American Journal of Obstetrics and Gynecology*, **119**, 749-754.

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Paul J. B. Slade, RAF Honington, nr. Bury St Edmunds, Suffolk.

British Journal of Urology (1978), **50**, 282

Ectopic Thoracic Kidney

Case Report

A man aged 69 was admitted with gross painless haematuria. Cystoscopy revealed a small bleeding papillary tumour in the bladder, which was resected. Intravenous pyelography revealed a normal right kidney but on the left side the kidney was located over the seventh to the tenth rib (Fig. 1). Selective renal angiography demonstrated a long renal artery emerging from the aorta at a normal level, bifurcating below the kidney and dividing into 4 to 5 branches (Fig. 2). The kidney itself looked oval in shape, slightly rotated with the lower pole slightly pushed laterally and upward. The intrarenal arterial distribution looked homogenous and no tumour circulation was seen. Cystoscopy 3 months later showed a normal bladder.

Comment

Intrathoracic kidney is a rare developmental anomaly—2 cases out of 15,919 autopsies of children (Moazzenzadeh *et al.*, 1977). Most intrathoracic kidneys function normally and require no medical or surgical treatment. Generally it is an incidental finding of a mass in the posterior lower thorax on a routine chest radiograph, mostly on the left side and of male preponderance (Ang and Chan, 1972). Diagnosis is by intravenous pyelography to differentiate from a hernia of the foramen of Bochdalek or any benign or malignant posterior mediastinal or diaphragmatic mass (Lundius, 1975).

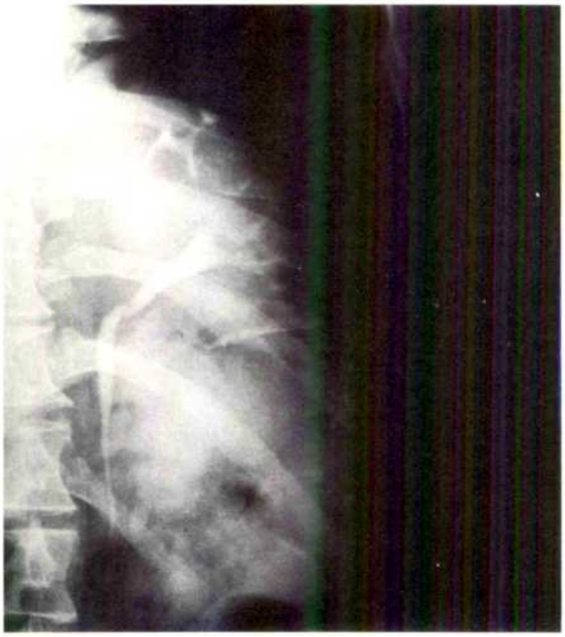

Fig. 1

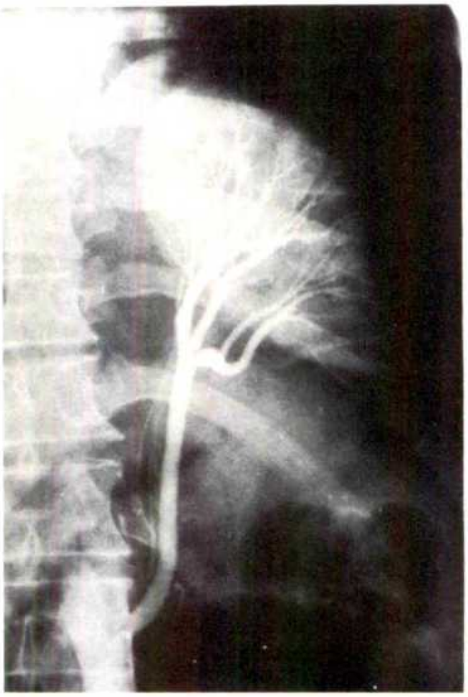

Fig. 2

References

Ang, A. H. and Chan, W. F. (1972). Ectopic thoracic kidney. *Journal of Urology*, **108**, 211-212.

Lundius, B. (1975). Intrathoracic kidney. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine*, **125**, 678-681.

Moazzenzadeh, A. R., Khodadadian, P. and Potter, R. T. (1977). The intrathoracic kidney. *Journal of Thoracic and Cardiovascular Surgery*, **73**, 480-482.

The Authors

E. Merimsky and M. Firstater, Department of Urology, Ichilov Hospital, University of Tel Aviv, Israel.

British Journal of Urology (1978), **50**, 283

Transverse Testicular Ectopia

Case Report

A boy of 3 years was admitted with a gradually increasing, painless swelling in the right inguinoscrotal region for 2 years, and absence of the left testis since birth. On examination there was a reducible inguinoscrotal swelling with positive cough impulse and negative transillumination test; 2 testicles with 2 separate cords were felt in the right side of the scrotum. The left side of the scrotum was empty and underdeveloped. No other testis could be felt in the left inguinal canal or on abdominal examination.

At operation, a complete hernial sac was opened and 2 normal-looking testes were found lying side by side in the fundus of the hernial sac. Each testis had its own epididymis and spermatic cord, which were joined by a mesentery (Fig.). The hernial sac was separated from the cord and ligated at the external inguinal ring. Exploration of the left inguinal and retroperitoneal area revealed no evidence of undescended testis. IVP done post-operatively showed no renal abnormality.

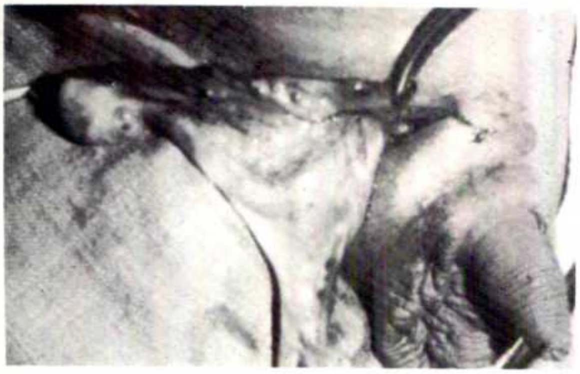

Fig.

Comment

Only 29 cases of transverse testicular ectopia have been reported in the world literature (Sastry *et al.*, 1974) of which 6 were on the right side. A familial incidence has been reported (Stauber, 1965). Although some authors have discussed the possible mechanism of this testicular anomaly, no definite cause has been defined (Gupta and Das, 1960).

References

Sastry, S. C., Venkateswarlu, K. and Hussain, B. A. (1974). Transverse testicular ectopia. *International Surgery*, **59**, 373-374.

Gupta, R. L. and Das, P. (1960). Ectopia testis transversa. *Journal of the Indian Medical Association*, **35**, 547.

Stauber, R. (1965). Familiäres Vorkommen von Dystopia testis transversa. *Zentralblatt für Chirurgie*, **90**, 621-625.

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H. L. Khamesra, A. S. Gupta and N. K. Malpani, Department of Surgery, R.N.T. Medical College, Udaipur (Rajasthan), India.

British Journal of Urology (1978), **50**, 284

Transplantation of a Horseshoe Kidney

Case Report

A 32-year-old man with head injury became a kidney donor. At laparotomy, the kidneys showed fusion of the lower poles but there was only 1 artery to each side, and 1 large vein on the left and 2 veins on the right. There was mild hydronephrosis bilaterally. After nephrectomy both arteries were perfused with Collins II, cold solution (Fig.) followed by division of the isthmus.

The left unit of the kidney was transplanted to a 45-year-old woman with end-stage kidney disease using a pyelo-pyelic anastomosis by Gil Vernet's technique (Gil Vernet and Caralps, 1968). The second recipient was a 44-year-old man and the right unit of the horseshoe kidney was implanted in the left iliac fossa with the classic reno-iliac vessels anastomosis and ureteroneocystostomy.

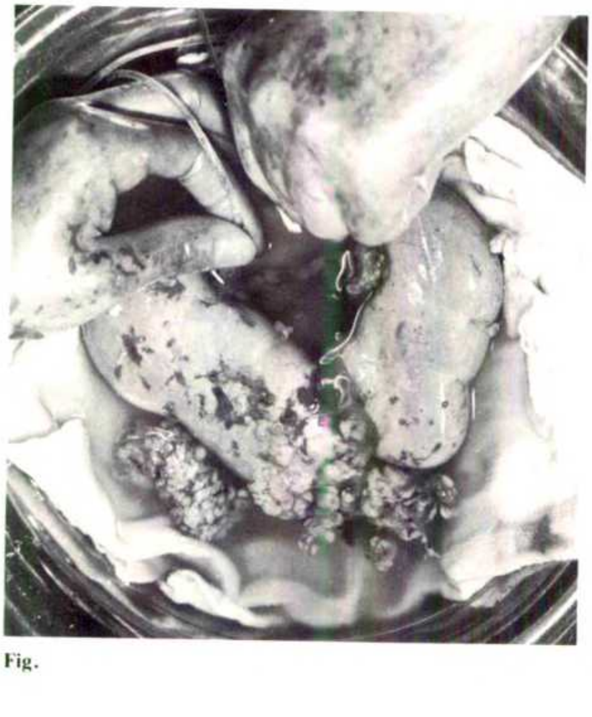

Fig.

The cold ischaemic times were 2 h and 40 min and 4 h, respectively. Function was poor initially and the recipient of the kidney with longer ischaemia needed dialysis. At discharge both patients had good kidney function a normal IVP with the Gil Vernet's technique and a mild hydronephrosis in the kidney transplanted with its pelvis and ureter.

Comment

Horseshoe kidneys, found in about 1 to 600 to 800 autopsies, are usually unsuitable for grafting because of multiple vessels and pelvi-ureteric problems leading to hydronephrosis, infection and stone formation (Campbell, 1970). An increasing need for cadaveric donors has led to kidneys with some anomalies being considered for transplantation. The horseshoe kidney is a major abnormality but in this case the kidneys were suitable for transplantation. As far as we could find this is the first reported case of successful horseshoe kidney transplantation to 2 recipients.

References

Campbell, M. F. (1970). Urology, 3rd edn. Edited by M. F. Campbell and J. H. Harrison. Philadelphia: W. B. Saunders Co., pp. 1447-1452.

Gil Vernet, J. M. and Caralps, A. (1968). Human Renal Transplantation. New Surgical Technique. Urologie internationalis, **23**: 201-223.

The Authors

Lauro Brandina, Altair J. Mocelin, Antonio M. A. Fraga and Gilson Lacerda, Avenida Bandeirantes 804, Londrina, Paraná, Brazil 86. 100.

British Journal of Urology (1978), **50**, 285

Angiofollicular Hamartoma of Castleman

Lateral deviation of the ureter is commonly due to primary or metastatic tumour in the retroperitoneal lymph nodes. We report an unusual retroperitoneal tumour displacing the ureter.

Case Report

A 22-year-old Punjabi male complained of left loin pain for 2 months. On examination there was a left-sided abdominal mass and a left varicocoele. Intravenous urography (Fig. 1) showed deviation of the left ureter. Haematological, biochemical and bacteriological investigations were normal.

At operation a retroperitoneal tumour which extended from left renal to left iliac vessels was completely excised after freeing the imbedded ureter from its lateral surface. Post-operative recovery was unremarkable.

Histology (Fig. 2) showed a vascular hamartoma in a skeleton of follicular lymphoid tissue with structures resembling Hassall's corpuscles: features characteristic of an angiofollicular hamartoma as described by Castleman and Towne (1954).

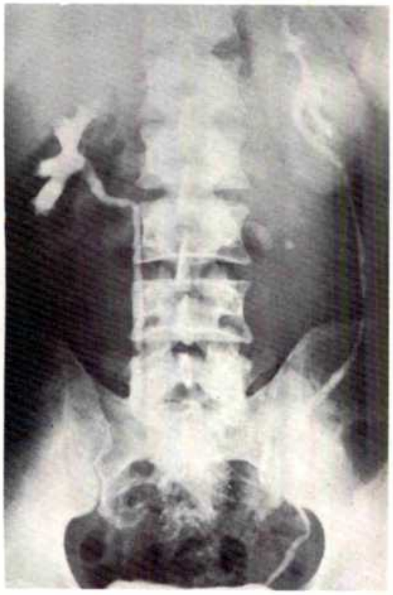

Fig. 1 Intravenous urogram showing deviation of the left ureter.

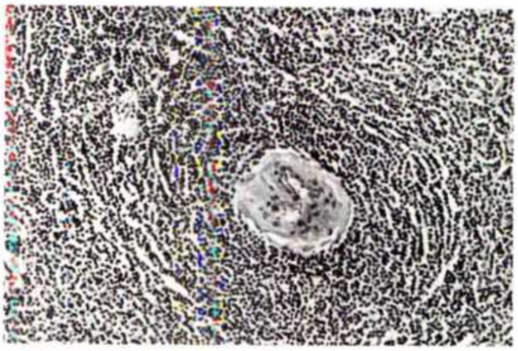

Fig. 2 Microscopical appearances of angiofollicular hamartoma (see text). (H & E. ×60.)

Comments

Approximately 100 cases of this benign tumour have been reported, usually occurring in the mediastinum, neck, shoulder girdle and, rarely, in the retroperitoneum. Treatment is total excision. There is 1 report of recurrence following incomplete excision. The effects of cytotoxic chemotherapy or radiotherapy are not reported. Of the 4 previous retroperitoneal cases reported only 2 involved the ureter, both without urological symptoms (Tung and McCormack, 1967; Block *et al.*, 1972).

References

Block, M. A., Morales, A. R. and Allen, H. M. (1972). Angiomatous lymphoid hamartomas. *Annals of Surgery*, **176**, 620-624.

Castleman, B. and Towne, V. W. (1954). Case 40011 (hyperplasia of mediastinal lymph nodes). *New England Journal of Medicine*, **250**, 26-30.

Tung, T. S. K. and McCormack, L. J. (1967). Angiomatous lymphoid hamartoma. *Cancer*, **20**, 525-536.

The Authors

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British Journal of Urology (1978), **50**, 286

Simple Chemotherapy for Bladder Lymphoma with Bilateral Hydronephrosis

Case Report

A 51-year-old civil servant developed painless swelling of his left leg. On examination there was widespread peripheral lymphadenopathy most marked in the inguinal region with oedema of the left leg and abdominal wall. On rectal examination there was rigidity of the anterior rectal wall. The creatinine clearance was 0.4 ml/s. An intravenous pyelogram demonstrated bilateral hydronephrosis without renal enlargement. At cystoscopy the bladder was deformed by "tumour" and the ureteric orifices were not visible. A biopsy of the bladder wall revealed histological changes consistent with malignant lymphocytic lymphoma. After 4 days' treatment with chlorambucil and prednisolone the left leg was almost free of oedema and the lymph nodes seemed smaller. An intravenous pyelogram after 8 weeks of treatment revealed no evidence of ureteric obstruction and the renal calices were no longer dilated. The creatinine clearance rose to 0.9 ml/s. After 32 months the clinical condition and biochemical state of the patient were excellent.

Comment

Non-Hodgkin bladder lymphoma is rare (Rosenberg *et al.*, 1961). The bilateral ureteric obstruction giving rise to bilateral hydronephrosis was presumably at bladder level. The effect of treatment was dramatic. We wish to emphasise the effectiveness of simple cytotoxic therapy.

Reference

Rosenberg, S. A., Diamond, H. D., Jaslowitz, B. and Craver, L. F. (1961). Lymphosarcoma: A review of 1,269 cases. *Medicine (Baltimore)*, **40**, 31-85.

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British Journal of Urology (1978), **50**, 287

Book Reviews

Clinical Pediatric Urology. Edited by P. P. Kelalis and L. R. King. Associate Editor A. B. Belman. Vol. 1: pp. xiii + 599 with approximately 400 illustrations. Vol. 2: pp. vii + 507 with approximately 270 illustrations. Philadelphia, London, Toronto: W. B. Saunders Company, 1976. Price £50.

By comparison with its adult counterpart, paediatric urology is a young speciality but like everything else which is young, it has shown a determined proclivity for growth. One measure of this growth is the appearance of an increasing number and size of the textbooks. The question that has to be asked is whether the scope of paediatric urology really warrants documentation on the impressive scale in 2 volumes used by Drs Kelalis and King and their co-editor. A cursory glance at just a few of the chapters in either of these volumes should soon confirm that such an effort was justified.

It is difficult to criticise this excellent work. The authors have studied their subjects thoroughly, sorted the important details from the literature and given comprehensive lists of references. Perhaps the first 3 chapters are the weakest, not because their writers have failed, but because they had the almost impossible task of trying to generalise on diffuse topics; the result is rather inconclusive and somewhat muddling. The chapter on anaesthetic management is very good. The reviewer could not find in the chapter on genital infections any mention of the duplex kidney as a possible cause of epididymitis, though it is mentioned in the section on ectopic ureter. The diagrammatic illustrations of the perineum in congenital cloaca bear little resemblance to the facts. There is no mention of the treatment of primary hyperoxaluria with magnesium hydroxide and there is a misprint on page 407. The chapters on the more controversial subjects such as distal urethral stenosis and bladder outflow obstruction are well balanced, both sides of the arguments being clearly presented.

Another feature of these volumes which is pleasing is the style of writing, which is clear, concise and reads easily. Even so, what does a radiologic technologist have that a radiographer doesn't, and how can something which is fundamental be more so by being a basic fundamental?

This work is a major contribution to the field of paediatric urology. The breadth of information is such that the experienced surgeon will find it useful in seeking data about the more unusual problems which he occasionally encounters and the postgraduate embarking on his training will be able to gain the basic knowledge that he needs. The description of operative techniques is minimal but the book is entitled "Clinical" and another volume would be required for this. Fortunately, by chance, another textbook on operative paediatric urology has been issued concurrently by another publisher: it is the ideal companionpiece.

Transactions of the American Association of Genito-Urinary Surgeons. Volume 68. Pp. 137. Baltimore: Williams & Wilkins Co., 1976. $15.00 (£10.50 approx.).

The Active Members of the American Association of Genito-Urinary Surgeons consist of most heads of departments and senior urologists in North America; the Corresponding Members are leading urologists in most western countries. This formidable group meet annually and the Transactions of the meeting are reported in a format similar to that of the *Journal of Urology*. However, an important difference lies in the Discussion sections: most of these are well worth reading, some are illuminating and often contain some very sharp but fair comment. The range of presentations is wide, so that here is an up-to-date slice of urology which would be a very useful volume for a departmental library.

Male Infertility. Richard D. Amelar, Lawrence Dubin and Patrick C. Walsh. Pp. xiv + 258. Philadelphia, London, Toronto: W. B. Saunders, 1977. £13.75.

This is a slim, readable book on male infertility. It could be of great value to the practising urologist who sees occasional cases of infertility but those main interest lies elsewhere. Practical solutions to many awkward problems are readily found by looking in the index: for example, retrograde ejaculation, hyperviscosity of semen or the orthodox Jewish lady with a short menstrual cycle!

The infertility expert is unlikely to find much that is new, although the references are good and include recent European as well as North American work.

Lecture Notes on Urology. John Blandy. Second edition. Pp. 320. Oxford: Blackwell Scientific Publications, 1977. £6.00.

In the second edition of this very useful book on elementary urology the references have been updated, a few of the diagrams improved and the length reduced by 11 pages. Owners of the first edition should regard it not as a new edition that renders their copy obsolete but as a reprint. Nevertheless we shall replace our copy of the first edition, not because it is out of date, but because it has been so popular among students, House Officers, nursing and ancillary staff that it is worn out.

Conferences and Courses

International Conference on Urinary Calculi

Perth, Western Australia. 4-8 August 1979

Further information may be obtained from the Convener: Assoc. Professor J. G. Brockis, International Conference on Urinary Calculi, University Department of Surgery, Royal Perth Hospital, Box X2213, G.P.O., Perth, Western Australia, 6001.

C.-E. Alken Prize 1978

A prize of 10,000 Swiss Francs is awarded each year to the author who submits the best unpublished work in the field of urology. The closing date for submission of manuscripts is 31 August 1978 and further particulars may be obtained from Professor E. J. Zingg, Department of Urology, Inselspital, CH-3010 Berne, Switzerland.

Request for Informal Proposals on Contraceptive Research and Development

The Program for Applied Research on Fertility Regulation (PARFR) at Northwestern University, Chicago, Illinois, is soliciting informal proposals from foreign and United States institutions for ***Applied Research*** projects in the field of fertility control. Proposals incorporating new ideas, techniques, and procedures, with the objective of developing new or improved methods of fertility control appropriate for use in developing countries will receive priority consideration. PARFR's interest in contraception includes the full range of fertility control methods—hormonal and other pharmacologic agents, mechanical and surgical. Contraceptive methods proposed for research support should be close to the stage of clinical applicability, although projects could include laboratory, animal and/or human investigation.

Further information can be obtained by writing or calling: Director of Administration, Program for Applied Research on Fertility Regulation, 1040 Passavant Pavilion, 303 East Superior Street, Chicago, Illinois 60611, USA. Telephone: (312) 649-2990.

Edinburgh Urological Festival

Edinburgh. 4-6 September 1978.

A postgraduate course in urology for consultants, senior registrars and registrars. Main topics: Bladder tumours, Infertility, Urinary diversion and replacement, Prostatic disease and Antibiotics.

Further particulars from: Urological Festival Secretary, Department of Surgery, University Medical School, Teviot Place, Edinburgh EH8 9AG.

Society of Uroradiology. First Annual Course

New York City, USA. 15-17 September 1978

For further information regarding this three-day course please contact Joshua A. Becker, MD, Department of Radiology, Box 1198, Downstate Medical Center, 450 Clarkson Avenue, Brooklyn, New York 11203, USA.

International Society for Cryosurgery

This Society was established in 1974 to foster the continued development and application of cryosurgery for the controlled cryogenic destruction of abnormal tissues.

An International Congress is held every third year where the latest results from all interested disciplines are presented and discussed.

Applications for membership from the Society's Secretary: Dr Marco Laudi, Via Nizza 39, 10125 Turin, Italy.

Organisers wishing to have details of their courses and conferences published in the Journal should send details to J. E. Newsam, Western General Hospital, Edinburgh EH4 2XU.

CURRENT UROLOGICAL LITERATURE: SELECT BIBLIOGRAPHY[1]

The List of Current Urological Literature is now arranged to correspond to the order in which papers are published in the *Journal, i.e.* in anatomical order beginning with papers on the kidney.

A general section is included at the end.

KIDNEY

General. Asymptomatic hematuria: diagnostic approach. (V. E. Pollak and B. S. Ooi.) *Postgrad. Med.* 1977, **62**, 115.

Renal haematurie—clinic and pathomorphology 5. (J. Brodehl and W. Thoenes.) *Monatschr. Kinderheilkd.* 1977, **125**, 754.

CT diagnosis and differential diagnosis of renal space occupying lesions. (L. Heuser *et al.*) *Roentgen-Blaetter*, 1977, **30**, 479.

The relation of the shape of renal papillae and of collecting duct openings to intrarenal reflux. (T. E. Tamminen and E. A. Kaprio.) *Br. J. Urol.* 1977, **49**, 345.

Selective renal phlebography in the diagnosis of renal pelvic and ureteric varices. (H. U. Braedel *et al.*) *Br. J. Urol.* 1977, **49**, 365.

Therapeutic renal infarction. (P. W. Bergreen *et al.*) *J. Urol.* 1977, **118**, 372.

Papillary necrosis pre-calyceal canalicular ectasia. Two aspects of the renal papilla which should be understood. (J. M. Vetel.) *Gaz. Méd. Fr.* 1977, **84**, 3391.

The kidney in the elderly. (P. Graux and M. Mestdagh.) *Ann. Anesth. Fr.* 1977, **18**, 439.

Examinations on renal morphology and function after urinary drainage operations in children with ecstrophia vesicae. (A. Schneider.) *Radiol. Diagn. (Berl.)* 1977, **18**, 211.

Compensatory renal hypertrophia in patients undergoing unilateral nephrectomy. (P. Mogensen *et al.*) *Scand. J. Urol. Nephrol.* 1977, **11**, 155.

The results of a renal phlebographie in the urographically unilaterally "nonfunctioning kidney". (J. Waigand and J. H. A. Müller.) *Dtsch. Gesundh.* 1977, **32**, 1559.

Renal endometriosis. (T. Gauperaa and H. Stalsberg.) *Scand. J. Urol. Nephrol.* 1977, **11**, 189.

Congenital Anomalies. Renal anomalies in fetal alcohol syndrome. (M. M. Debeukelaer *et al.*) *J. Pediatr,* 1977, **91**, 759.

Horseshoe and pelvic kidneys associated with abdominal aortic aneurysms. (F. Ezzet *et al.*) *Am. J. Surg.* 1977, **134**, 196.

Horseshoe kidney—ultrasonic demonstration. (H. J. Mindell and E. A. Kupic.) *Am. J. Roentgenol.* 1977, **129**, 526.

Association of renal and ureteral malformations—embryogenic hypothesis. (C. C. Schulman.) *J. Urol. Néphrol.* 1976, **82**, 420.

Hereditary (familial) renal disease—clinical and genetic studies. (P. R. Kenya *et al.*) *South. Med. J.* 1977, **70**, 1049.

Familial pheochromocytoma—rare case of hydronephrosis and hydroureter in 2 generations. (D. B. Spring and A. J. Palubinskas.) *Br. J. Radiol.* 1977, **50**, 596.

Bifid pelvis with blind ending. (K. Takahashi *et al.*) *J. Urol.* 1977, **118**, 97.

Unilateral small kidney. (H. L. Neiman *et al.*) *J.A.M.A.* 1977, **238**, 971.

Trauma. Penetrating renal injuries—peculiar problem of conservation of renal parenchyme. (H. M. Seybold.) *J. Urol. Néphrol.* 1976, **82**, 395.

Closed renal trauma. (J. M. Smith and J. D. O'Flynn.) *Br. J. Surg.* 1977, **64**, 753.

Renal trauma in the child. (J. P. Jablonski *et al.*) *J. Urol. Néphrol.* 1977, **83**, 598.

Traumatic arteriovenous shunt in region of major branches of a kidney. (J. Flamm and M. Hahn.) *Unfallheikunde,* 1977, **80**, 375.

Controversial aspects of blunt renal trauma. (A. J. Wein *et al.*) *J. Trauma,* 1977, **17**, 662.

The management of blunt injuries of the urinary tract. (V. Marshall.) *Aust. N.Z. J. Surg.* 1977, **47**, 548.

Renal angiography and the management of severe closed renal trauma. (D. I. Moss and R. Freeman.) *Aust. N.Z. Surg.* 1977, **47**, 462.

Surgical management of major renal trauma: review of 102 cases treated by conservative surgery. (M. A. Hai *et al.*) *J. Urol.* 1977, **118**, 7.

Infections. Perinephritic abscess 19 years after intentional ureteral ligation. (D. J. Mehan and M. J. Chehval.) *J. Urol.* 1977, **118**, 460.

Changing clinicopathological pattern of abscesses in or adjacent to kidney. (J. J. Malgieri *et al.*) *J. Urol.* 1977, **118**, 230.

Antibiotic treatment of renal carbuncle. (M. Schiff *et al.*) *Ann. Intern. Med.* 1977, **87**, 305.

Renal actinomycosis. (R. J. Morgan *et al.*) *Eur. Urol.* 1977, **3**, 307.

Hematuria in primary chronic pyelonephritis. (E. M. Aryeva *et al.*) *Ter. Arkh.* 1977, **49**, 26.

Priorities in prevention of pyelonephritis. (C. M. Kunin.) *Am. J. Dis. Child.* 1977, **131**, 1281.

Acute renal failure secondary to pyelonephritis. (A. H. Greenhill *et al.*) *Clin. Nephrol.* 1977, **8**, 400.

Diffuse xanthogranulomatous pyelonephritis in children: unrecognised variant. (F. H. Bagley *et al.*) *J. Urol.* 1977, **118**, 434.

Emphysematous pyelonephritis. (C. K. Carris and J. D. Schmidt.) *J. Urol.* 1977, **118**, 457.

Xanthogranulamatous pyelonephritis, report of recent cases. (E. Sanchezcortes *et al.*) *Med. Clin. (Barcelona)*, 1977, **69**, 189.

Xanthogranulomatous pyelonephritis. (R. Romerogonzalez *et al.*) *Med. Clin. (Barcelona)*, 1977, **69**, 260.

Calculi. Recurrences after conservative surgery for renal lithiasis. Review of 600 operations (1955-73). (D. Grasset *et al.*) *J. Urol. Néphrol.* 1977, **83**, 647.

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[1] Titles in this list have been taken from those listed in *Current Contents: Clinical Practice* published by Institute for Scientific Information, Philadelphia.

Staghorn calculi in children. (F. F. Bartone and J. H. Johnston.) *J. Urol.* 1977, **118**, 76.

Urinary hydroxyproline concentration in primary hyperparathyroidism with and without renal stones. (E. Sommer-Tsilenis.) *Eur. Urol.* 1977, **3**, 231.

Methyldopa and renal stones: a retrospective study. (L. E. Ramsay.) *Med. J. Aust.* 1977, **2**, 495.

6-mechanisms of renal stone production—study of hypercalciurias stone formers with Ca-45. (B. Pinto *et al.*) *Med. Clin. (Barcelona),* 1977, **69**, 141.

Nontraumatic para-aortic lymphocele complicating nephrolithiasis. (E. A. Hyson *et al.*) *Radiology,* 1977, **124**, 648.

Treated and untreated recurrent calcium nephrolithiasis in patients with idiopathic hypercalciuria, hyperuricosuria or no metabolic disorder. (F. L. Coe.) *Ann. Intern. Med.* 1977, **87**, 404.

Adjuvant antimicrobial therapy with renal calculus surgery. (L. J. Harrison *et al.*) *J. Urol.* 1977, **118**, 233.

Do Australian aborigines suffer from renal tract calculi? (E. M. Bateson) *Aust. N.Z. J. Med.* 1977, **7**, 380.

Localisation of intrarenal calculi during surgery. (W. H. Boyce.) *J. Urol.* 1977, **118**, 152.

Circulatory Disorders. Bilateral renal artery aneurysms: in situ and extra corporeal repair. (I. R. Gough *et al.*) *Aust. N.Z. J. Surg.* 1977, **47**, 660.

Surgical treatment of dysplastic lesions of renal arterial branches. (J. M. Dubernard *et al.*) *J. Urol Néphrol.* 1976, **82**, 399.

Selective renal artery embolization. (A. M. Hachman *et al.*) *J.A.M.A.*, 1977, **238**, 1534.

Renal allograft artery stenosis. (R. Munda *et al.*) *Am. J. Surg.* 1977, **134**, 400.

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Seasonal variations in urinary crystals. (P. C. Hallson and G. A. Rose.) *Br. J. Urol.* 1977, **49**, 277.

Case Reports

280 Metastasis from Renal Carcinoma to a Phalanx of the Hand
J. A. de Oliveira Filho, E. Silveira and J. L. C. Marins

281 Successful Pregnancy in a Patient with Previous Ectopia Vesicae
G. D. Miller and P. J. B. Slade

282 Ectopic Thoracic Kidney
E. Merimsky and M. Firstater

283 Transverse Testicular Ectopia
H. L. Khamesra, A. S. Gupta and N. K. Malpani

284 Transplantation of a Horseshoe Kidney
L. Brandina, A. J. Mocelin, A. M. A. Fraga and G. Lacerda

285 Angiofollicular Hamartoma of Castleman
C. L. Kennedy, G. Williams and J. E. Castro

286 Simple Chemotherapy for Bladder Lymphoma with Bilateral Hydronephrosis
M. J. Farr, D. W. W. Newling and C. Raper

287 Book Reviews

288 Conferences and Courses

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British Journal of Urology

June 1978 Volume 50 Number 4

Original Articles

217 Pyeloplasty in Infants and Children with Particular Reference to the Method of Drainage Post-operatively
A. M. K. Rickwood and D. Phadke

222 Prediction of Renal Recovery in Hydronephrotic Kidneys
Ahmed Ibrahim and Hassan Abu Asha

227 The Value of Provocative and Acute Urography in Patients with Intermittent Loin Pain
P. Davies, K. A. Woods, C. M. Evans, W. M. Gray and A. E. Kulatilake

233 Ureteric Reimplantation for Vesico-Ureteric Reflux in the Adult
A. Dounis, M. Dunn and P. J. B. Smith

237 The Site of Recurrence of Non-Infiltrating Bladder Tumours
B. H. Page, V. B. Levison and M. P. Curwen

243 Results of Prolonged Bladder Distension as Treatment for Detrusor Instability
A. W. Pengelly, T. P. Stephenson, E. J. G. Milroy, C. G. Whiteside and R. T. Turner-Warwick

246 An Objective Assessment of the Unstable Bladder of Psychosomatic Origin
W. K. Frewen

250 Biofeedback in the Treatment of Detrusor Instability
L. Cardozo, S. L. Stanton, J. Hafner and V. Allan

255 Ultrasonic Lithotriptor for Urethral and Bladder Stones
Salah El Fahiq and D. M. Wallace

257 Endourethral Urethroplasty: A Simple Method for Treatment of Urethral Strictures by Internal Urethrotomy and Primary Split Skin Grafting
Silas Pettersson, Bjorn Asklin and Claes-Goran Bratt

262 The Mucosal Electrosensitivity Threshold (MST): A Test for use in Conjunction with Electronic Stimulation in Urinary Incontinence in Women
H. Kiesswetter and J. Flamm

264 Technique and Results of the Colonic Conduit, Continent by Means of a New Magnetic Stoma Seal: An Experimental Study
E. Wilhelm, A. Sigel, Th. Hager and G. Hening

269 Design of a Urodynamic Questionnaire
Linda Cardozo, Stuart L. Stanton and A. E. Bennett

275 Carcinoma of the Penis
A. A. Khezri, M. Dunn, P. J. B. Smith and J. P. Mitchell

[*Continued on Inside Back Cover*]

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10 Penis
11 Scrotum and scrotal contents
12 Intersexuality
13 Infertility
14 Adrenal glands; Retroperitoneum
15 Chemical injuries
16 Renal physiology
17 Stone formation
18 Diagnostic procedures
19 Urinary tract infections
20 Genitourinary tuberculosis
21 Parasitic disease
22 Hypertension
23 Renal failure
24 Dialysis
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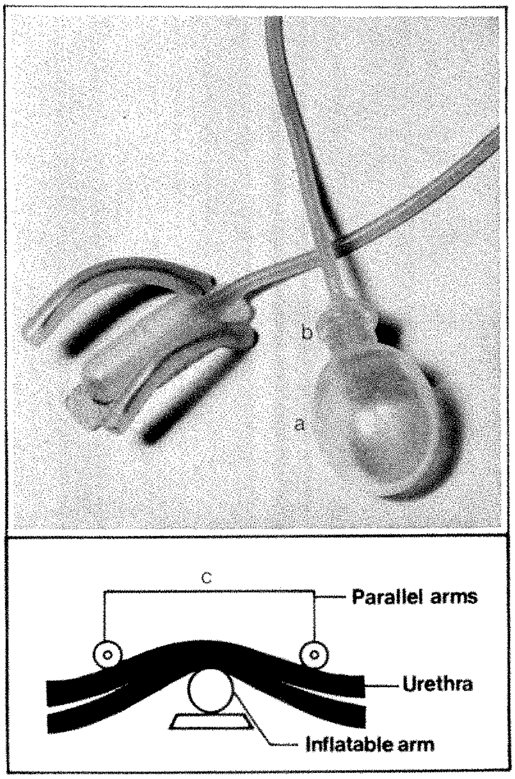

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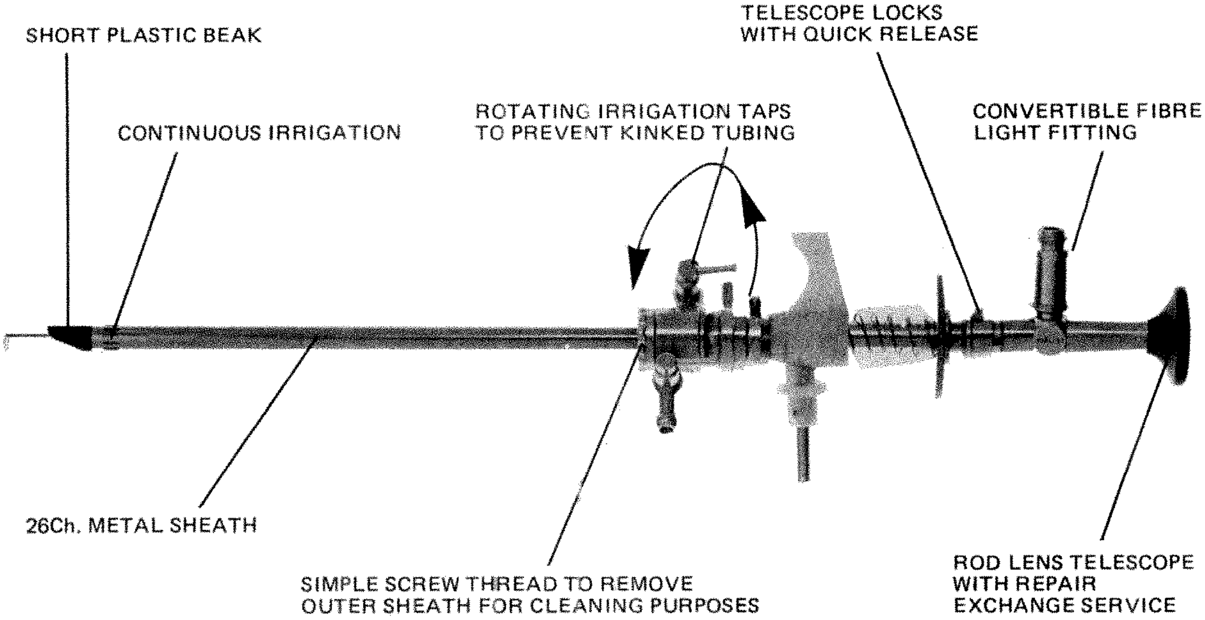
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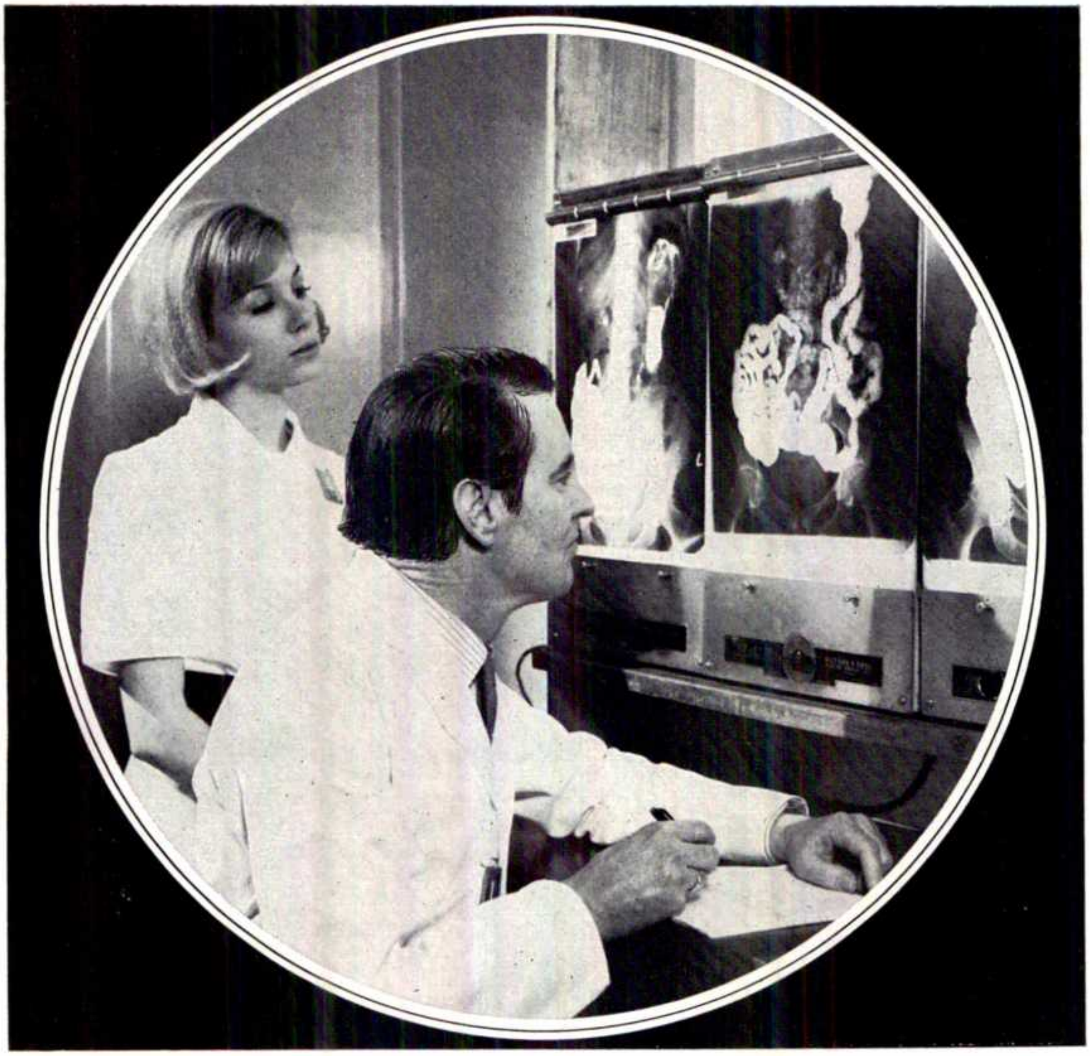

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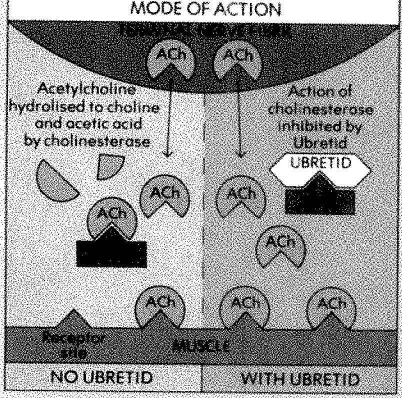
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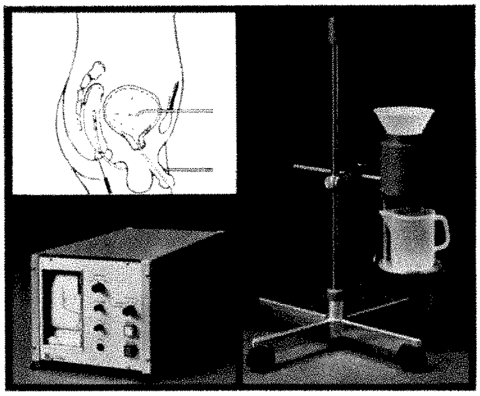

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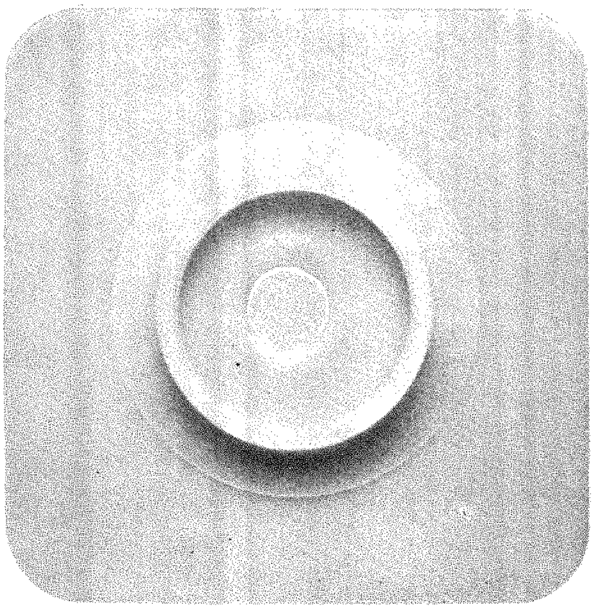

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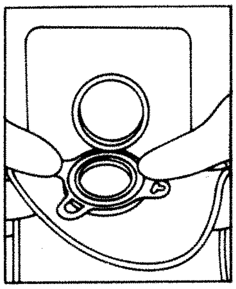

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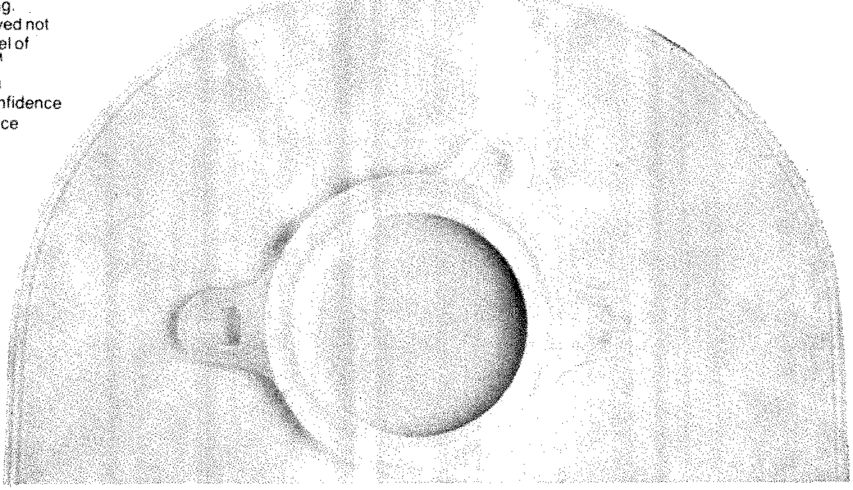

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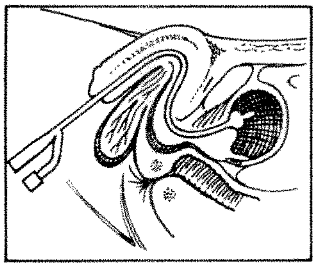

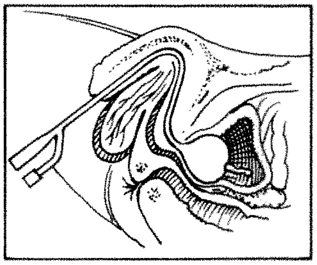

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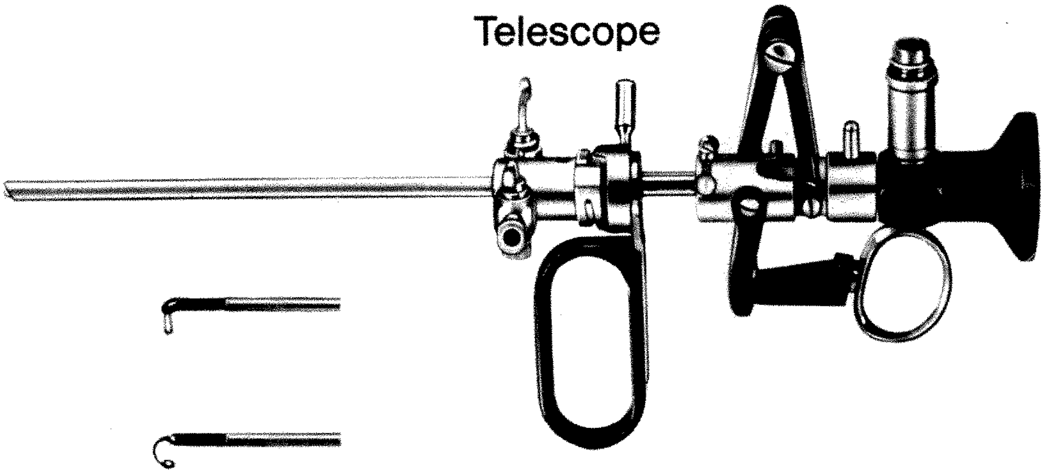

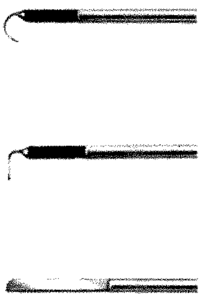

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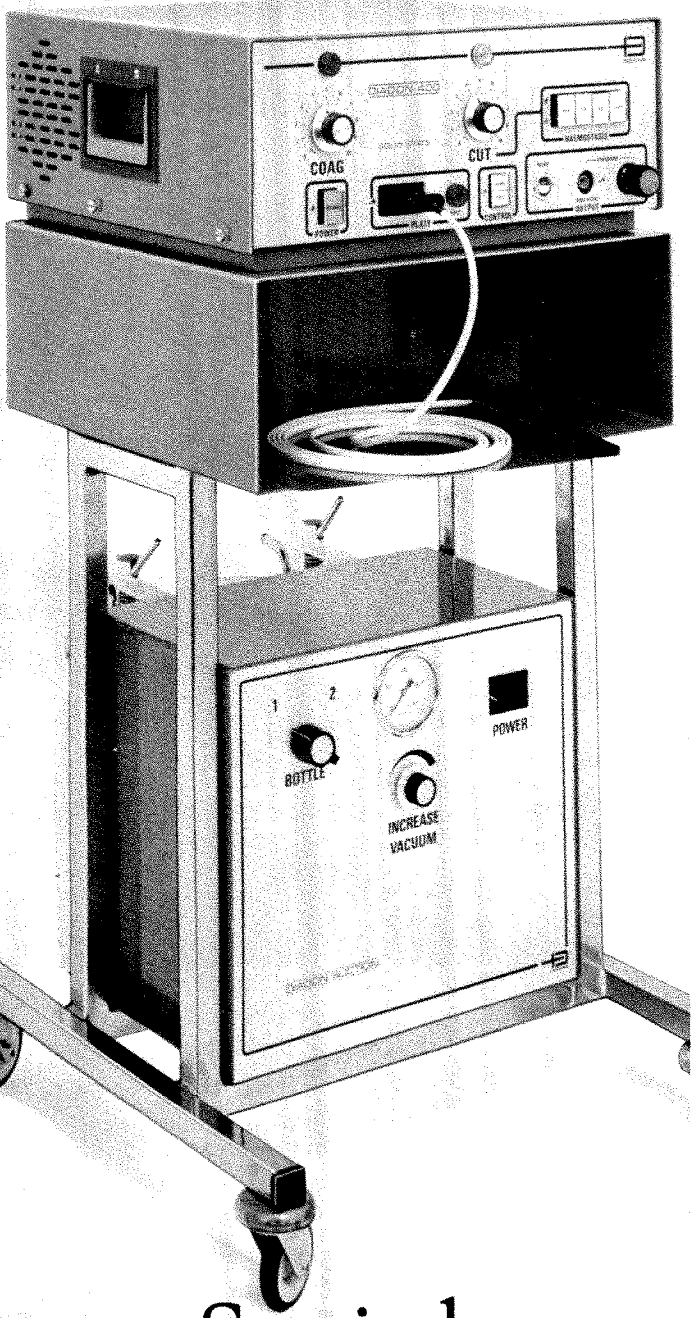

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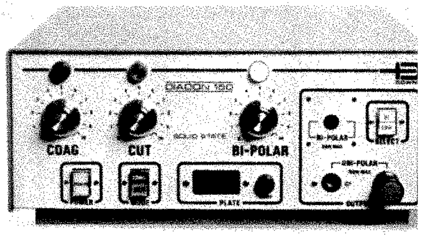

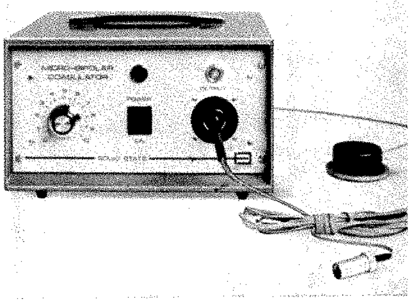

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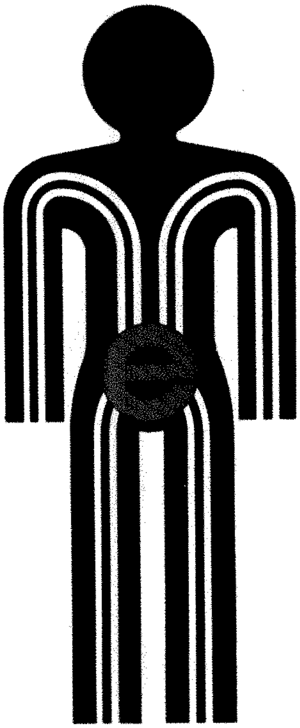

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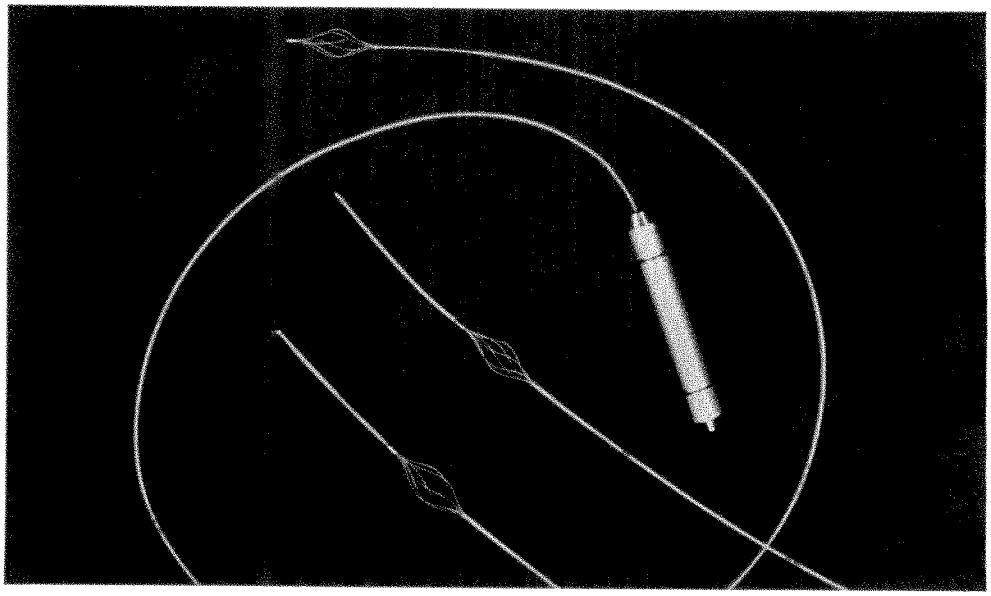

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British Journal of Urology (1978), **50**, 289-293

Radiograph Measurements and Contralateral Renal Size in Primary Pelvic Hydronephrosis

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Summary—Renal size was estimated from the radiographs in 47 cases of primary pelvic hydronephrosis. The area of functioning renal tissue of the side *opposite* to the disease was greater in patients with severe hydronephrosis treated by pyeloplasty, compared with those with moderate disease ($P < 0.05$). This suggests that compensatory hypertrophy had occurred in the contralateral kidney. This finding did not appear to affect the outcome of pyeloplasty. It is suggested that the finding of compensatory hypertrophy in the kidney opposite to a severe hydronephrosis is not a contra-indication to conservative surgery.

According to Anderson (1962) even a thin shell of renal cortex may be preserved when operating for primary pelvic hydronephrosis and very few nephrectomies should be required. Hydronephrotic kidneys with such a thin cortex may be radiologically non-functioning or severely diseased and yet worth preserving. The problem remains to identify pre-operatively which of the severely diseased kidneys will be worth preserving, and with this in mind it was thought worthwhile to see if useful information could be gained by measuring the size of kidneys on radiographs. Notley and Beaugie (1973) wished to do this but were unable to because many of the radiographs were old and of too poor a quality. Radiological techniques have now improved and outlines are clearer. The aim of this study, therefore, was to identify any radiographic changes in size of either diseased or normal kidneys which might assist in the pre-operative assessment of severely hydronephrotic kidneys.

Patients and Methods

Forty-seven patients with primary pelvic hydronephrosis presented between 1970 and 1976, all under the care of one consultant. Thirty were treated by pyeloplasty, 13 by primary nephrectomy, and 4 conservatively.

Intravenous pyelograms were performed using standard equipment with 40 ml of Conray 420. Nearly all films were taken with a tube-film distance of 100 cm. All the pyeloplasties were of the Anderson-Hynes type using 3/0 plain catgut. Splint catheters across the anastomosis were used in 5 cases, and "Redivac" suction drains to the site of the anastomosis in all cases.

The areas were measured by carefully tracing the outlines of the kidney on the IVPs and counting squares over graph paper (excluding the pelvicaliceal system). The resulting area was called the area of "functioning renal tissue" (FRT). The 5 or 10 min film sufficed with normal kidneys, but hydronephrotic kidneys with fainter outlines and delayed pelvicaliceal filling required measurements on 2 films, subtracting from the area of the nephrogram that of the pelvicaliceal system at its fullest.

Standard correlation and t-tests of small samples were used to analyse the results. Normal distribution of each main sample to 95% confidence was proved by the use of probability paper.

Results

There were 31 males and 16 females; the mean age of the males (30 years SD 19.5) was less than the mean age of the females (44 years SD 20), but this difference was not significant. Disease was more common on the left (26 cases) than the right (21 cases). These differences were due to the preponderance of male left-sided disease under the age of 20 years. There was 1 case of bilateral disease. There were 2 associated congenital abnormalities—horseshoe kidney and

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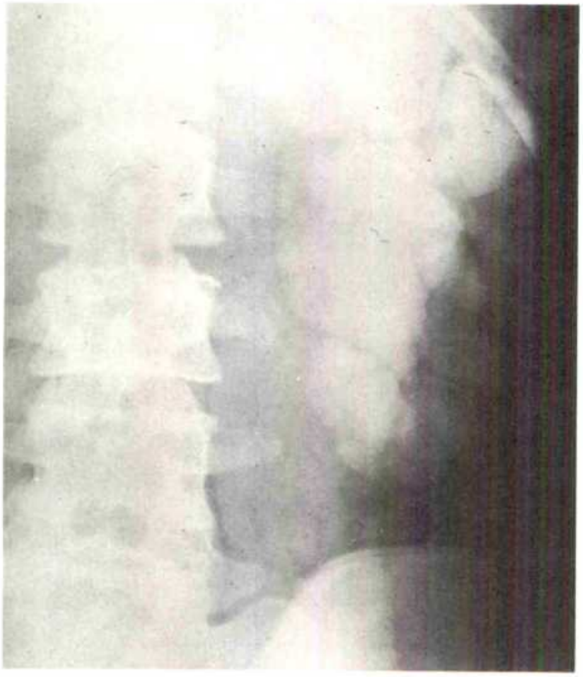

Fig. 1 Four hour film of boy aged 16 years. Severe hydronephrosis.

duplex kidney—and 2 patients had associated calculi.

Of those patients treated by nephrectomy, 7 had radiologically non-functioning kidneys, 4 were severely diseased radiologically, and 2 were mildly diseased but the kidney was removed for other reasons.

Severe and Moderate Hydronephrosis

The kidneys treated by pyeloplasty were divided into 2 groups—those with severe and those with moderate disease.

There were 2 radiologically non-functioning kidneys which had some radiological function restored by pyeloplasty; 7 further pyeloplasties pre-operatively showed a faint or absent nephrogram, delayed pelvicaliceal filling and an indistinct ball pyelogram which took up to 24 h to empty, and no radiological ureteric filling. These 9 cases were considered severe; an example is shown in Figure 1. Delayed but clear filling of an extra-renal pelvis was not considered severe, since it has been pointed out that an extra-renal pelvis probably protects the renal substance from damage (Roberts and Slade, 1964); an example of this is shown in Figure 2. The table shows the results of pyeloplasties comparing severe with moderate disease, and they are the same. The follow-up was between 6 months and 5 years, with 1 non-attendance.

Radiograph Measurements

The outlines of the severely diseased kidneys were too ill-defined for measurement; even the severe ones which could be measured were so indistinct that there was much room for error, and it was therefore felt that such measurements were too unreliable. Hence there is no subsequent discussion on the results obtained from measuring the diseased kidneys. However, there was no problem measuring the *contralateral* kidneys in all the radiographs.

Before the pyeloplasty the length of the diseased kidney was greater ($P<0.05$) and the area of FRT was less ($P<0.01$) than the contralateral side, and this was not changed by operation, a result which one would expect.

The area of FRT before operation of the side *opposite* to the disease was greater in patients subsequently treated by nephrectomy than in those subsequently treated by pyeloplasty. This difference was also found after excluding the

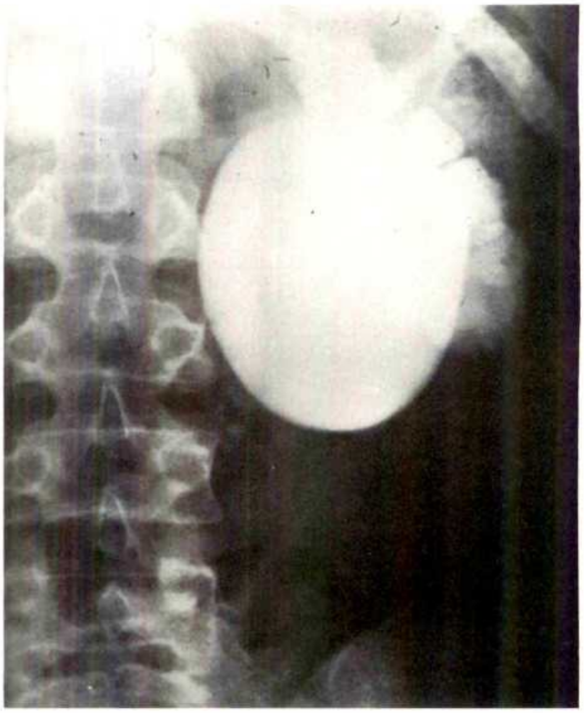

Fig. 2 Five hour film of boy aged 12 years. *Not* severe hydronephrosis (see text).

patients aged less than 17 years, whose small kidneys might have been so because of immaturity. These differences were not significant ($P<0.1$) but became so after excluding the 2 patients who had mildly diseased kidneys removed ($P<0.05$).

The nephrectomy group was small (7 cases), so 6 further intravenous pyelograms were obtained, all those available from nephrectomies performed in 1974 for other reasons. Four showed a non-functioning kidney due to carcinoma, and 2 showed a normal remaining kidney at least 1 year after nephrectomy. The measurements on the functioning sides showed the same difference from the pyeloplasty group ($P<0.001$) and in this case the lengths were also greater ($P<0.01$). These kidneys were also bigger than the primary pelvic hydronephrosis nephrectomies group (*contralateral* sides), even excluding the 2 where mildly diseased kidneys were removed, though not significantly ($P<0.1$).

These results are summarised in Figure 3.

On the available radiographs, for patients aged more than 17 years the *contralateral* sides of the severely diseased pyeloplasty cases were compared with those of the moderate cases. The severely diseased group had bigger contralateral kidneys than those of the mild group ($P<0.05$). This result is depicted in Figure 4, which also shows that, with 1 exception, even those patients with the biggest contralateral kidneys had good results from their pyeloplasties.

Discussion

The interpretation of these results is simple at face value. The good kidneys have hypertrophied when the bad kidney is either functioning but grossly diseased, or non-functioning. Contralateral compensatory hypertrophy with functioning but grossly hydronephrotic kidneys has been noted before (Davies *et al.*, 1972) but not quantified.

The difference between the 2 nephrectomy groups suggests that there was further potential for hypertrophy in the good kidneys of the primary pelvic hydronephrosis group, and this could mean that either there was residual unrecognised function in the excised kidneys, or that the mere presence of a kidney, though non-functioning, prevents maximal compensatory hypertrophy on the other side. It has been suggested before that the latter may happen

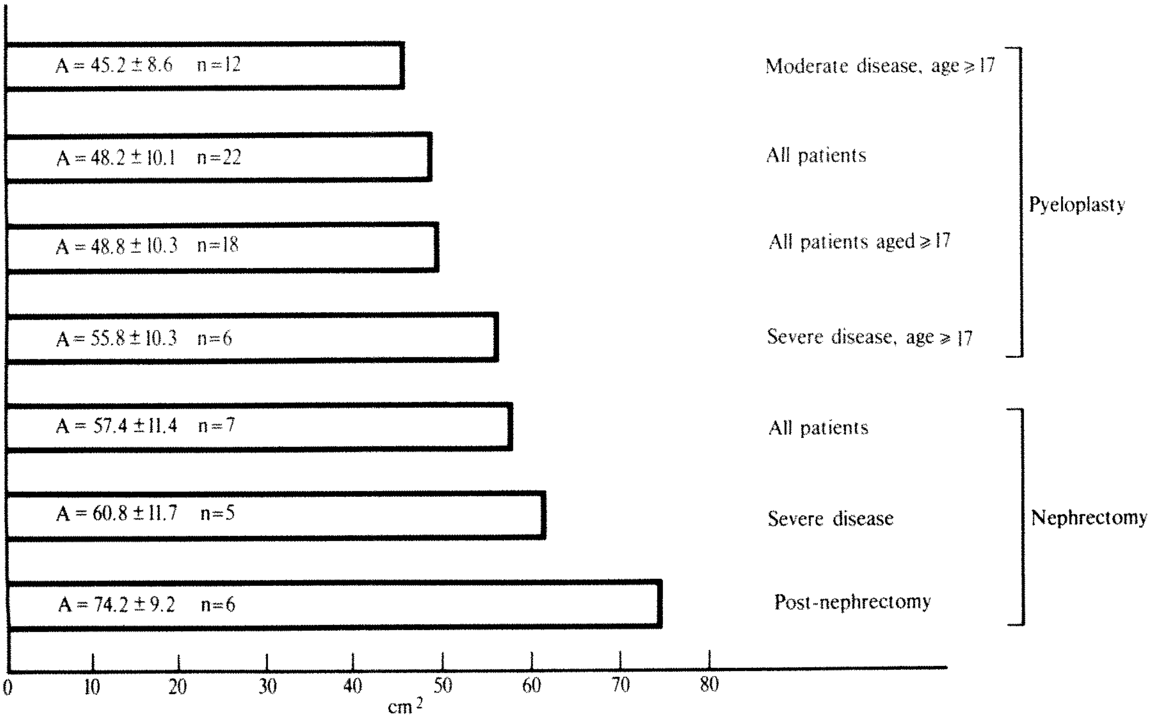

Fig. 3 Area FRT of contralateral kidneys. A = area ± standard deviation. n = number of radiographs.

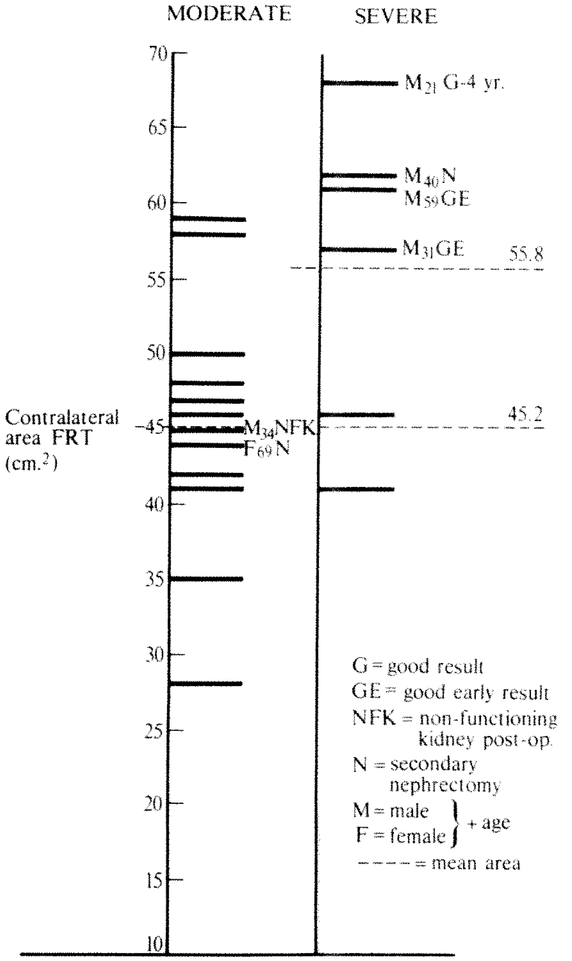

Fig. 4 Contralateral areas and results of pyeloplasties (patients aged > 17 years).

(Friedman *et al.*, 1942), possibly because of renin secretion (Schaffenberg *et al.*, 1954). The numbers in these groups were too small, however, to make the factors discussed below likely to be inoperative.

Both radiological area and length have been shown to correlate well with renal volume and weight for a given position of the kidney in the body (Griffiths *et al.*, 1975). However, sex, body-weight, age (Rouiller and Muller, 1969), and even dietary protein (Brod, 1973) affect the volume of the kidney, and hence the radiograph area measurements. In addition, there may be projectional errors due to variations in the way the kidney lies in the body. Griffiths *et al.* (1975), studying cadaver kidneys, showed that the longitudinal axis of the kidney is angled upper pole backwards between 8 and 20 degrees, and that this could influence the apparent length on a radiograph by up to 1 cm. The transverse axis is less variable, the kidney being angled 40 to 45 degrees back into the paravertebral gutter. Variation of radiographic area due to these angle variations was not assessed, but it would probably be more, as area was correlated strongly with the product of length and width and is therefore affected by variation in both axes. Probably less important, it has not been proved that the contralateral kidneys in this study were normal in area, though it would seem reasonable to suppose so in view of there being no bilateral disease on the radiographs measured. Variability in the tube-film distance of the X-ray machine is not thought to be a factor as nearly all the films were taken at 100 cm.

If, having considered this, the above interpretation of the results is accepted, the question remains, "Does the presence of compensatory hypertrophy on the contralateral side influence the outcome of a pyeloplasty?".

Of the 3 patients who lost their kidneys following pyeloplasty (Fig. 4), 1 had a large contralateral kidney, and this could possibly have reflected a particularly poor, diseased kidney and thus have been a factor in the failure of the operation; but the other 2 did not have particularly large contralateral kidneys, and other factors must have been responsible.

Of the 4 severely diseased pyeloplasty cases with the biggest contralateral kidneys (3 being

Table 1 Results of 30 Pyeloplasties

	No.	*Age (yr ± SD)*	*Symptoms lost*	*Symptoms insignificant*	*No FU*	*Symptoms lost (%)*	*Temporary urine leak*		*Urine leak (%)*	*Nephrectomy (2°)*
							< 10/7	> 10/7		
Severe disease	9	26 ± 15	7	1	0	78	1	3	44	1
Moderate disease	21	30 ± 15	16	2	1	76	1	6	33	1

(SD = Standard Deviation; FU = Follow-up) bigger than all the others) (Fig. 4), 3 had good results. Two of these are early and one would have to await the long-term follow-up to be sure. However, it has been reported that an early good result tends to be maintained or even improved (Notley and Beaugie, 1973). Therefore the results suggest that, if anything, contralateral hypertrophy does not affect the outcome of pyeloplasty.

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The Relationship Between Urinary Bilharziasis and Urolithiasis in the Sudan

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Summary—Nine hundred and ninety-seven Sudanese patients presenting to a urological unit in Khartoum were divided into a group consisting of 144 patients with a history or evidence of urinary bilharziasis and a second group of 853 patients with no history or evidence of this disease. Thirty-one per cent of the patients with bilharziasis and 32% of those without were found to have urinary calculi. In the bilharzial group there were recurrent stones in 7% compared with 12.4% in the non-bilharzial group. In the bilharzial group the stones were renal in 63.6%, ureteric in 27.3% and vesical in 9.1%, while in the non-bilharzial group 57% were renal, 30% ureteric and 13% vesical. Comparison of the incidence, rate of recurrence and site of stones in both groups suggests that urinary bilharziasis does not contribute to the high incidence of urolithiasis in the Sudan.

Both bilharziasis and urolithiasis are common in the Sudan. Fibrosis and strictures leading to urinary stasis and infection may complicate urinary bilharziasis (Talib, 1972; Smith *et al.*, 1974) and are factors which may provoke stone formation. They may account for the high incidence of urinary stone found. This study examines the validity of this assumption by comparing the pattern of occurrence of urinary calculi in both the bilharzial and non-bilharzial groups.

Patients and Methods

Nine hundred and ninety-seven patients presenting to a urological unit in Khartoum between July 1975 and July 1977 were studied. One hundred and forty-four of these either gave a previous history or had evidence of urinary bilharziasis, whilst the remaining 853 patients had neither history nor evidence of this disease. Diagnosis of bilharziasis in the first group was based on 1 or more of the following:

1. Past history of urinary bilharziasis.
2. Radiological features of bilharzial complications such as lower ureteric stricture (Fig. 1) and bladder calcification.
3. Cystoscopic evidence of bilharziasis including sandy patches, follicles and granulomatous polyps.
4. Identification of bilharzial ova in the urine or histologically in biopsy specimens from the bladder or from the ureter at operation.

Both groups of patients were studied and compared in respect of:

1. Incidence of urolithiasis.
2. Incidence of recurrent urolithiasis.
3. Site of stones in the urinary tract (kidney, ureter, bladder).

Results

Bilharzial Group (Table 1)

Twenty-three patients in this group were found to have ureteric strictures. Fifteen of these were histologically confirmed as bilharzial in origin and the remaining 8 had a previous history of the disease. Sixteen patients had cystoscopic evidence of bilharzial involvement of the bladder either in the form of follicles, sandy patches or chronic infection, whilst 5 patients had histologically proven bilharzial polyps in the bladder. Of 4 patients with urethral stricture, 1 was confirmed to be bilharzial in origin at urethroplasty whilst the other 3 gave a previous history of the disease and no other obvious cause for the pathology.

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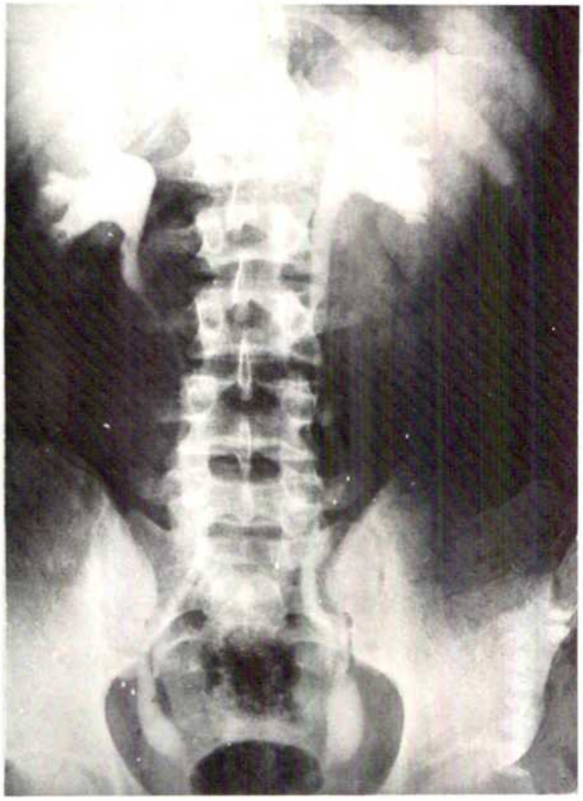

Fig. 1 Intravenous urogram showing bilateral bilharzial stricture of the lower ureter.

Three patients had bladder neck obstruction histologically shown to be a sequel to bilharziasis and 1 patient had calcification of the bladder demonstrable on X-ray. There was 1 case of squamous cell carcinoma of the bladder in association with vesical bilharziasis. Five patients were found with active urinary bilharziasis on urine examination, whilst the remaining 86 patients gave a previous history of the disease but had no demonstrable lesion either on urography or cystoscopy.

Non-Bilharzial Group

There were 853 patients in this group. Two hundred and thirteen had urological conditions which were potentially calculogenic either as a result of promoting biochemical change or stasis in the urine (Table 2).

Stone Incidence in Bilharzial and Non-Bilharzial Groups

In the bilharzial group 44 of 144 patients (31%) had urolithiasis (Table 1) compared with 274 of 853 patients in the non-bilharzial group (32%). The general incidence of urolithiasis in the 2 groups is therefore similar.

Table 1 Bilharzial Group—Stone Incidence and Site

Stage of bilharzial disease	*Total*	*Cases with stones*		
		Renal	*Ureteric*	*Vesical*
Ureteric stricture	23	5	3	–
Bilharzial cystitis (follicles, sandy patches) and infection	16	1	1	–
Bilharzial polyp	5	–	1	–
Calcified bladder	1	–	–	–
Bladder cancer	1	–	–	–
Bladder neck obstruction	3	–	1	–
Urethral stricture	4	1	–	–
Positive urine analysis	5	1	–	–
Positive past history	86	20	6	4
Total	144	28	12	4

Patients within the bilharzial group with pathological sequelae of this disease causing urinary stasis or inflammation, focal or general, numbered 52 and of these 13 (25%) were found to have stones (Table 3).

In the non-bilharzial group, stones were found in 47 of the 213 patients with potentially calculogenic disease (22.5%) (Table 2).

Incidence of Recurrence

In the bilharzial group 3 of 44 patients (7%) had

Table 2 Non-Bilharzial Group—Frequency of Potential Calculogenic Disease and Stone Incidence

	Total	*Cases with stones*
Cystinuria	4	4
Polycystic kidney	2	1
Hypercalcaemia	2	2
Pelvi-ureteric obstruction	14	6
Malrotated kidney with hydronephrosis	7	2
Horseshoe kidney	5	4
Pelvic kidney	10	2
Renal tuberculosis	1	1
Nephrocalcinosis	2	2
Ureteric stricture—traumatic	6	1
Neurogenic bladder	1	–
Senile prostate	100	16
Bladder neck obstruction	10	2
Carcinoma prostate	5	–
Urethral stricture	43	4
Haematocolpos with hydronephrosis	1	–
Total	213	47

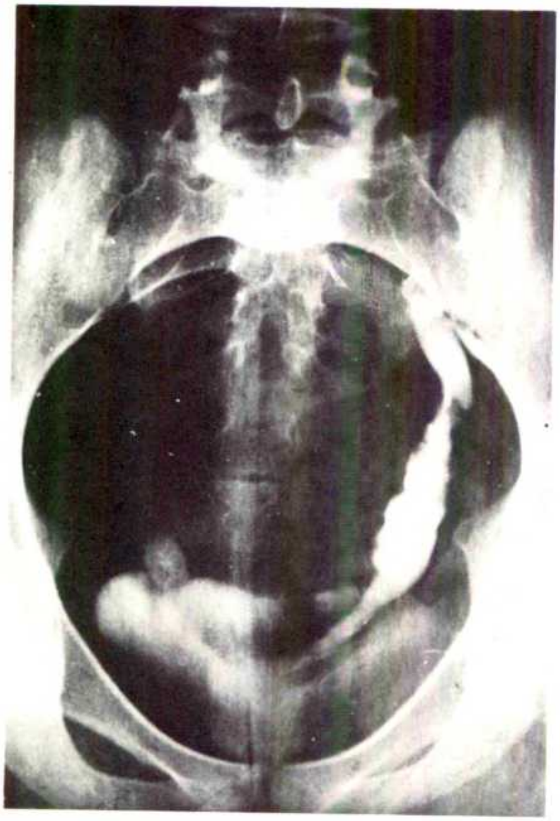

Fig. 2 Intravenous urogram showing a bilharzial stricture of the lower left ureter and a stone in the lower right ureter.

recurrent urolithiasis. In 1 there was a demonstrable ureteric stricture and the stones were sited in the kidney. The recurrent calculi in the other 2 were ureteric and in these there was a previous history of bilharzia but no anatomical evidence of ureteric stasis.

In the non-bilharzial group there was recurrence in 31 of 274 patients (12.4%). Recurrence was therefore more common in the patients without bilharziasis but this was not statistically significant ($P > 0.5$).

Site of Stones (Table 4)

In the bilharzial group 28 patients (63.6%) had renal stones whilst 12 (27.3%) had ureteric and 4 (9.1%) had bladder stones. In comparison, the non-bilharzial group had 155 patients with renal stones (57%), 83 (30%) with ureteric and 36 (13%) with vesical calculi. Ureteric and bladder stones were therefore slightly more common in the non-bilharzial group, whilst renal stones were more common in patients with evidence or a history of bilharzia, but in neither case was the difference significant.

Table 3 Incidence and Site of Stones in Bilharzial Patients with Post-Inflammatory Complications

Lesion	*Total*	*Cases with stones*		
		Renal	*Ureteric*	*Vesical*
Ureteric stricture	23	5	3	–
Bilharzial cystitis, sandy patches and follicles	16	1	1	–
Bilharzial polyps	5	–	1	–
Calcified bladder	1	–	–	–
Urethral stricture	4	1	–	–
Bladder neck obstruction	3	1	–	–
Total	52	7	6	–

Discussion

The common urinary complications of bilharziasis are granulomatous inflammation which leads subsequently to fibrosis and scarring with their sequelae of urinary stasis and infection, all of which can predispose to urolithiasis (Parquis *et al.*, 1972). Talib (1972) noted that both ureteric and bladder stones occurred frequently in bilharzial patients in Iraq, whilst Ghorab (1962) attributed the occurrence of ureteric stones in Egyptians to previous urinary bilharziasis. Lehman *et al.* (1973) also found a high incidence of urinary calculi in bilharzial patients but in these and other studies there does not appear to have been any comparison with the incidence in an unaffected population.

In this study the incidence of urinary calculi has been compared in both a bilharzial and a non-bilharzial group and has been found similar, *i.e.* 31 and 32% respectively. This suggests that bilharzia and its sequelae in the urinary tract do not play a significant role in the pathogenesis of urolithiasis in the Sudanese.

Recurrent stone formation occurred in 3 (7%)

Table 4 Site of Urinary Stones in Bilharzial and Non-Bilharzial Patients

	Total	*Kidney*	*Ureter*	*Bladder*
Bilharzial patients	44	28 (63.6%)	12 (27.3%)	4 (9.1%)
Non-bilharzial patients	274	155 (57%)	83 (30%)	36 (13%)

of the bilharzial stone formers and only 1 of these had a demonstrable lesion (ureteric stasis) which could be expected to promote conditions favourable for stone recurrence. The frequency of recurrence was greater in the non-bilharzial group (12.4%) and this may be explained by the presence in this group of patients of conditions such as cystinuria, nephrocalcinosis and either urinary infection or urinary tract stasis, the persistence of which could be expected to be accompanied by recurrent stone formation. These factors therefore appear to have had more influence in respect of recurrence than bilharzia or its sequelae.

Fibrosis as a complication of urinary bilharzia occurs most commonly in the lower ureter and in the bladder (Talib, 1972). As a result of scarring in these sites and resultant obstruction and urinary stasis, stones in bilharzial patients might be expected to occur more commonly in the ureter and the bladder. The findings in this series were that ureteric and vesical stones were slightly more common in the non-bilharzial group (30 and 13%) than in the bilharzial (27.3 and 9.1%). In contrast, renal stone was more common in bilharzial patients (63.6%) than in the non-bilharzial (57%). This further suggests that the stones found in the bilharzial patients were more often a coincidence than a complication of the primary disease.

Analysis of the bilharzial patients with demonstrable complications of this disease (Table 3) showed that although more than half had vesical or urethral lesions, none of these had bladder stones. Whilst 23 had ureteric strictures, only 8 of these (34.4%) had upper urinary tract stones. Of the other 32 instances of upper urinary tract stone in this group (Table 1) 4 were in the presence of one of the manifestations of bilharzial cystitis, 2 in accompaniment of lower urinary tract obstruction, whilst the majority (26) occurred in those with a previous history but, no demonstrable residual lesion of bilharziasis. This suggests that the majority of upper urinary tract stones in the bilharzial group were formed for reasons other than bilharzia.

Study of the non-bilharzial group showed that 213 of the 853 patients (25%) had diseases which could predispose to urolithiasis (Table 2). Of these, 47 (22.5%), were found to have stones. In other words, in the non-bilharzial group, of a total of 274 stone formers only 47 (17%) had a possible aetiological factor, the remaining 227 (83%) being idiopathic in origin. Of the metabolic abnormalities which may be associated with idiopathic stone disease, uric acid disorder may play a prominent role in the Sudan, as is suggested by the recent work of Ibrahim *et al.* (1977).

In conclusion, the study of both bilharzial and non-bilharzial groups of patients in the Sudan suggests that the high incidence of urolithiasis is unlikely to be the result of bilharzia or its complications. Several other reports support this finding and in particular Loutfi *et al.* (1974) considered that bilharzia played little, if any, part in the aetiology of bladder stone disease in Egyptian children although the infestation was common. Urinary calculi are also rare in bilharzial patients in Rhodesia (Honey and Gelfand, 1960) and in Natal (Chapman, 1966).

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Coagulum Pyelolithotomy

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Summary—In 25 patients undergoing pyelolithotomy a supplementary coagulum technique has been used. Initial difficulties were found in the preparation, instillation and extraction of the coagulum, but with experience a satisfactory technique has been developed.

The type of stone situation most likely to benefit from coagulum pyelolithotomy would seem to be where there is a small, mobile stone or stone fragment lying in a calix or in a wide renal pelvis.

The operation of pyelolithotomy aims to achieve the complete removal of all stone fragments from the renal pelvis and calices. Though often a straightforward surgical procedure, there may be technical difficulties in the removal of all stone fragments. This is particularly true where there are small, mobile, free stones or fragments of larger stones. On these occasions the operation may be time-consuming and may result in much trauma to the kidney. Thus a wide range of supplementary techniques has been developed to assist the surgeon in pyelolithotomy. These include the irrigation of the renal pelvis and calices, X-ray studies of the exposed kidney, nephrotomy, partial nephrectomy and renal cooling techniques using temporary vascular clamping and multiple nephrotomy incisions.

Despite these additional techniques small stones or fragments of stones are often left behind and, on occasion, these residual stone particles may contribute to the recurrence rate that is notoriously associated with simple pyelolithotomy. In order to reduce the incidence of incomplete removal of stone particles the additional supplementary technique of coagulum pyelolithotomy has been studied.

Coagulum pyelolithotomy was originally described by Dees in 1943, who has since given a composite review of his contribution to this technique (Dees, 1955). Patel (1973) offered further evidence of the value of coagulum pyelolithotomy and recently added further evidence of the continuing value of this technique (Patel, 1976).

Patients

Over a 6-month period all patients admitted for pyelolithotomy were considered for the coagulum technique. These patients had a wide range of renal stones, varying from the small solitary mobile type to the staghorn variety. In the majority a coagulum pyelolithotomy was performed. In this way it was possible to develop the technique of preparing the coagulum and to define those cases in which a coagulum pyelolithotomy was a useful aid in the complete removal of the stone.

Methods

Materials

The materials used (fibrinogen and thrombin) were obtained from the National Blood Transfusion Service, through the hospital pharmacist. One of us (M.D.) has also obtained supplies through Lister Blood Products. Patel (1976) obtained his materials through Behringwerke, Marburg, W. Germany. It is important to obtain these materials from the correct sources since commercially prepared thrombin and fibrinogen are not always suitable for this coagulum technique.

Preparation of Coagulum

The technique employed was as suggested by Patel (1976). One gram of human fibrinogen was dissolved in 20 ml of normal saline at a temperature of 37°C and maintained at this temperature for a minimum period of 15 min. A second solution of 200 units of human thrombin, dissolved in 3 ml of normal saline plus 1 ml of 5.5% calcium

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chloride, was also prepared at 37°C and maintained for a period of 15 min at this temperature. Both solutions were prepared in sterile galley pots, the temperature being maintained in a blood warmer machine. The 2 solutions can be made up at the start of the operation as periods in excess of 15 min make no difference to the overall effectiveness of the subsequent coagulum. When the stage is reached for inserting the coagulum, both solutions are mixed and immediately drawn up in a 50 ml bladder washout plastic syringe. The timing of this stage is critical, as the 2 solutions will begin to coagulate within 30 s of mixing. Ideally, the mixing, drawing up and instillation into the renal pelvis should be complete within 10 s.

Instillation Technique

The renal pelvis should be exposed so as to give access for a wide pyelotomy incision. A 10 F.G. Foley catheter with a 5 ml balloon is inserted into the renal pelvis through a small stab incision and inflated and the catheter then pulled back against the pelvis in order to seal the stab incision. Before instilling the coagulum the renal pelvis and calices should be emptied of urine and washed out with saline; no air should be allowed to enter the collecting system. The coagulum mixture is injected through the catheter so as to over-distend the renal pelvis. Where there is a small or intrarenal type of pelvis which precludes the use of this technique, the catheter can be inserted through a separate ureterotomy incision, approximately 1 cm distal to the pelvi-ureteric junction, and the ureter around the catheter compressed by a rubber sling during the instillation.

Extraction

The coagulum sets in approximately 7 min. At this stage a standard pyelotomy incision is made and the coagulum removed, together with the entrapped stone material. Normally, the coagulum can be removed intact using a stone forceps. Occasionally, caliceal elements of the coagulum may break off, though often quite large casts of coagulum can be extracted even through a narrow caliceal neck, owing to the elastic nature of the coagulum itself. Where fragments of the coagulum do break off, these can be extracted separately with stone forceps or washed out by forcible irrigation.

Results

This technique has now been used in 25 cases of pyelolithotomy; 19 were considered to have failed for a variety of reasons (Table 1). The majority of failures were during earlier experience with the technique and 5 of the 6 successful procedures were carried out on the last 7 occasions. The technique was considered successful when it was felt that the coagulum had contributed to the complete removal of all stone material from the kidney (Fig. 1). In 2 cases, X-ray studies of the coagulum revealed stones which had not been detected on previous X-ray examination.

Discussion

It is now over 30 years since coagulum pyelolithotomy was first attempted (Dees, 1955). Patel (1976) has recorded 145 instances of coagulum pyelolithotomy in the world literature but he also described a personal series of 271 coagulum pyelolithotomies carried out between 1963 and 1975. His series had a technical failure rate of only 6.6% and showed a high success rate in total removal of stones and removal of undetected stones. Patel has also raised the possibility of infective hepatitis from the materials used for the coagulum and has advocated the prophylactic use of gamma globulin; there were no cases of hepatitis in our present series.

In our series of 25 cases there was a high incidence of failure. This was due mainly to a lack of awareness of the exact requirements for coagulum formation. Care must be taken in the preparation of the 2 solutions, which should be kept at 37°C, and the use of a blood warmer machine has solved this problem. These solutions must also be made up in plenty of time, to allow for a minimum of 15 min at 37°C.

Table 1 Reasons for Failure in Coagulum Pyelolithotomy

Failure of coagulum formation	
(*a*) No coagulum formed	3
(*b*) Premature coagulation	6
Instillation technique	
(*a*) Extrusion of coagulum	5
(*b*) Inadequate distension of pelvis with air leakage	2
Extraction technique	
(*a*) Fragmentation of coagulum	2
(*b*) Fibrin remnants	1
	19

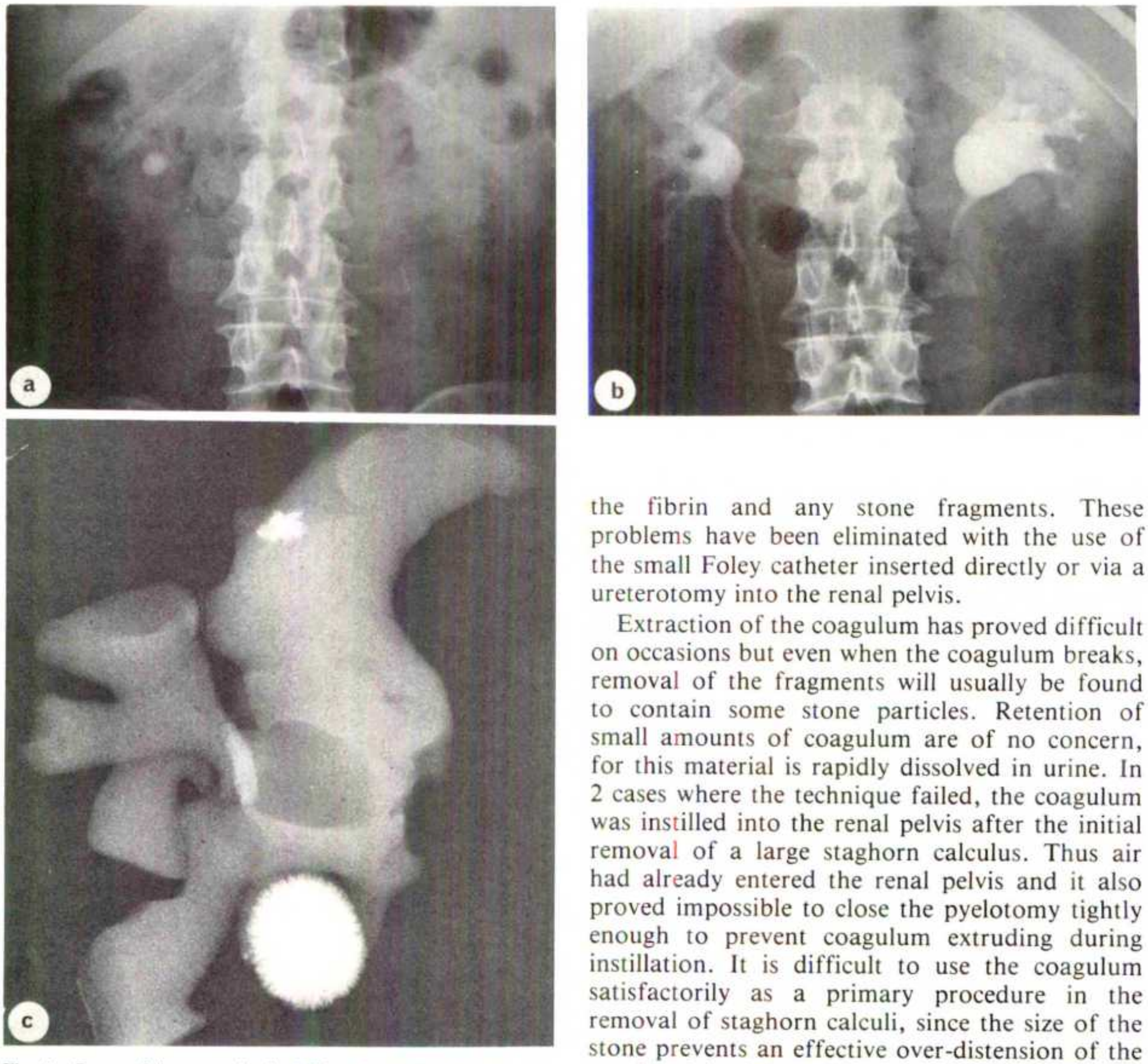

Fig. 1 Successful removal of additional small mobile stone. (*a*) Plain X-ray showing 1 large and 1 small pelvic stone. (*b*) IVP showing capacious renal pelvis. (*c*) X-ray of coagulum showing both stones trapped and successfully removed.

A wide variety of instillation techniques has been tried and experimentation with various techniques has contributed to the failure rate. The use of an aspiration needle, a drawing-up quill and a 10 F.G. Nelaton catheter, each inserted through a purse string suture in the renal pelvis, proved unsatisfactory. It was impossible to over-distend the renal pelvis due to leakage of the coagulum mixture, and there was a tendency for air to leak into the collecting system. Air may rise to the top of the calices and prevent proper contact between the fibrin and any stone fragments. These problems have been eliminated with the use of the small Foley catheter inserted directly or via a ureterotomy into the renal pelvis.

Extraction of the coagulum has proved difficult on occasions but even when the coagulum breaks, removal of the fragments will usually be found to contain some stone particles. Retention of small amounts of coagulum are of no concern, for this material is rapidly dissolved in urine. In 2 cases where the technique failed, the coagulum was instilled into the renal pelvis after the initial removal of a large staghorn calculus. Thus air had already entered the renal pelvis and it also proved impossible to close the pyelotomy tightly enough to prevent coagulum extruding during instillation. It is difficult to use the coagulum satisfactorily as a primary procedure in the removal of staghorn calculi, since the size of the stone prevents an effective over-distension of the renal pelvis. Though coagulum pyelolithotomy has been recommended by Patel (1976) in the surgery of staghorn calculi, no success was obtained in the 2 patients in this small series. In addition, he also recommends this coagulum technique as a means of fixing stones prior to nephrotomy or partial nephrectomy. None of the patients in this series was in this group.

In this preliminary study coagulum pyelolithotomy has been found to be a useful supplementary technique where there are (1) small, free stones lying in a large renal pelvis, (2) solitary caliceal stones, (3) crumbly stones with large amounts of stone debris in the renal pelvis. The results of the study, where the technique has been successful, are in accord with the views expressed by Patel (1976) in his review of a much larger and technically more successful series.

With proper case selection and adequate technical preparation and instillation, the use of a fibrin coagulum does seem to be a worthwhile supplementary procedure in pyelolithotomy.

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Calculi in Renal Transplants

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Summary—Three patients who underwent live donor renal transplantation subsequently developed calculi in their allografts.

Hypercalcaemia and secondary hyperparathyroidism were present in 2 cases and these were treated by subtotal parathyroidectomy.

Urinary stagnation and infection were contributory factors in the third case and reimplantation of the ureter was necessary.

In all patients no further calculi have developed following treatment and allograft function remains satisfactory.

Development of calculi in successful renal allografts is extremely uncommon, for only 8 separate cases have been reported (Leapman *et al.*, 1976).

Hypercalcaemia and secondary hyperparathyroidism were predisposing factors in most of them. Parathyroidectomy decreased the size of existing calculi and reduced parenchymal calcification as well as preventing the development of recurrent calculi. Hyperplasia and hyperfunction of the parathyroids are well recognised complications of chronic renal disease and they persist for a while after transplantation. Increased levels of serum calcium accompany this change in endocrine function and must be considered to predispose to the development of renal calcification and calculi. Although 30% of patients have increased parathyroid function and hypercalcaemia after transplantation, progression of renal calcification is rarely seen. This may be explained by the transient nature of the hypercalcaemia and the intensive investigation and treatment that such patients undergo.

In our unit, 3 of 276 patients who have undergone renal transplantation have developed calculi in their grafts. Features of their presentation and management are described.

Case Reports

Case 1. A 24-year-old female began haemodialysis in August 1969 because of end stage renal failure secondary to pyelonephritis. At this time plasma urea was 33 mmol/l (normal value 2.5-6.5 mmol/l); potassium 6.8 mmol/l (3.8-5.2 mmol/l); plasma creatinine 1529 μmol/l (55-125 μmol/l) and GFR was 3 ml/min. Serum calcium was 2.4 mmol/l (2.15-2.65 mmol/l); phosphate 3.27 mmol/l (0.8-1.4 mmol/l); alkaline phosphatase 9 IU/l (30-130 IU/l) and (total) serum protein 59 g/l (65-80 g/l). The urinary calcium excretion rate was 6 mmol/24 h (5 mmol/24 h). There were no radiological features of secondary hyperparathyroidism.

She underwent a 10-h session of haemodialysis twice weekly with a bath calcium concentration of 1.5 mmol/l until April 1970, when she received a live donor transplant from her father. After transplantation she was taking aluminium hydroxide 10 ml qds, neutral phosphates mixture 30 ml tds and Vitamin D 1 mg/day.

In March 1971 intravenous urography demonstrated a calculus in the upper caliceal region of the transplanted kidney. Serial serum calcium estimations had shown a progressive rise with peak values of between 3 mmol/l and 3.5 mmol/l, total serum protein 59 to 66 g/l. There were no radiological changes of parathyroid bone disease. Subtotal parathyroidectomy was performed in 1971 and, histologically, all 4 glands showed diffuse hyperplasia. Post-operatively, serum calcium fell to 2.6 mmol/l, total serum protein was 64 g/l, phosphate 0.96 mmol/l and alkaline phosphatase 4 IU/l. Urinary calcium excretion was 4.7 mmol/24 h.

In November 1971 pyelolithotomy was carried out. Transplant biopsy at this time showed no histological evidence of rejection or nephrocalcinosis.

A further calculus was demonstrated radiologically in the kidney in August 1972, but this passed spontaneously, although she continued to have repeated episodes of urinary infection.

At re-assessment in January 1975, plasma urea was 4.5 mmol/l, plasma creatinine 96.8 μmol/l, urine volume was in excess of 3 l/day with no proteinuria and the GFR was 50 ml/min. Intravenous urography,

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micturating cystography and cystoscopy were all normal. Serum calcium was 2.1 mmol/l, phosphate 0.5 mmol/l, and alkaline phosphatase 37 IU/l. Total serum protein was 67 g/l. Urine was infected with *E. coli* and she is maintained on long-term co-trimoxazole.

Case 2. This 39-year-old man developed end stage renal failure due to accelerated hypertension in February 1970. Plasma urea was 33.2 mmol/l, plasma creatinine 994.4 μmol/l and GFR 3 ml/min. Serum calcium was 1.25 mmol/l, total serum protein 48 g/l, serum phosphate 1.43 mmol/l and alkaline phosphatase 10 IU/l. There was heavy proteinuria, 0.54 g/24 h (less than 0.05 g/24 h). Low protein diet and antihypertensive therapy failed to control his condition and bilateral nephrectomy was performed with good effect. He began twice-weekly haemodialysis for a period of 12 weeks.

In July 1971 he received a live donor renal transplant from his brother. Apart from a vesicocutaneous fistula which was successfully treated by antibiotics and urethral catheter drainage, post-operative recovery was unremarkable.

At the time of discharge he was normotensive and on no treatment. Plasma urea was 8.3 mmol/l, plasma creatinine was 79.2 μmol/l and GFR 58 ml/min. Serum calcium was 2.55 mmol/l, total serum protein 51 g/l, phosphate 0.58 mmol/l and alkaline phosphatase 8 IU/l.

In November 1971 he passed a calculus *per urethram* and investigation at this time showed hypercalcaemia and hypercalciuria. Blood calcium was 3.05 mmol/l, total serum protein 63 g/l, phosphate 0.7 mmol/l and alkaline phosphatase 9 IU/l. Calcium 24 h excretion was 10 mmol/l. There was no radiological evidence of hyperparathyroidism, although both femoral heads showed osteoporotic changes. At urography, intramural calcification in the lower end of the ureter was observed but no further calculi were seen. Cystoscopy showed calcareous debris at the ureteric orifice. Catheterisation of the ureter was unsuccessful and he was started on hyoscine butylbromide 10 mg qds, forced oral diuresis and low calcium intake. Three further calculi were passed urethrally in the next 2 weeks and radiology of the transplant showed no residual calculi.

On a low calcium diet his hypercalcaemia and hypercalciuria became normal. However, subtotal parathyroidectomy was undertaken in December 1971 and all 4 glands showed diffuse hyperplasia. Post-operatively the serum calcium fell dramatically to 0.9 mmol/l and oral calcium supplement and Vitamin D were needed. Recovery was otherwise uneventful and he was discharged taking calcium gluconate 600 mg 3 times daily and Vitamin D 2 mg daily.

In January 1972 hypercalcaemia recurred. Serum calcium was 3.27 mmol/l, total serum protein 61 g/l, phosphate 1.18 mmol/l and alkaline phosphatase 13 IU/l. The urinary calcium excretion rate was 12.85 mmol/24 h. Urography showed another calculus in the lower part of the transplanted ureter and one in the prostatic urethra. Calcium supplements were stopped and the 2 calculi removed by ureteric catheterisation and by vesico-lithotomy. During the next 6 weeks serum calcium stabilised at 2.2 mmol/l, total serum protein 63 g/l, phosphate at 1.18 mmol/l, and alkaline phosphatase 10 IU/l without medication. Urinary calcium excretion rate was 1 mmol/24 h. An asymptomatic urinary infection during this admission resolved with antibiotics. Further calculi have neither been demonstrated radiologically nor passed in the urine. His most recent serum creatinine is 96.8 μmol/l.

Case 3. This 39-year-old male patient developed end stage renal failure due to chronic glomerulonephritis in December 1973. Plasma urea was 23.2 mmol/l, plasma creatinine 1230.8 μmol/l and GFR less than 1 ml/min. The serum calcium was 2.2 mmol/l, total serum protein 52 g/l, serum phosphate 2.1 mmol/l and alkaline phosphatase 52 IU/l. Regular dialysis was started immediately and continued until January 1974, when he received a live donor renal transplant from a sister. Post-operative recovery was uneventful and, at that time, his plasma urea totalled 11.5 mmol/l, plasma creatinine 114.4 μmol/l, serum calcium 2.4 mmol/l, total serum protein 60 g/l, phosphate 0.6 mmol/l and alkaline phosphatase 65 IU/l. The GFR was 33 ml/min.

In May 1974 a mild rejection episode was diagnosed but this responded rapidly to antirejection therapy. There was urine infection with *Proteus vulgaris* and intravenous urography showed hydroureter and hydrocalicosis due to a calculus at the ureterovesical junction of the transplant ureter. At this time serum calcium was 2.37 mmol/l, total serum protein 61 g/l, phosphate 1.22 mmol/l and alkaline phosphatase 68 IU/l. Urinary calcium and phosphate excretion rates were 4 mmol/24 h (5 mmol/24 h) and 23.25 mmol/24 h (30 mmol/24 h). There were no radiological changes of hyperparathyroidism. Ureterolithotomy was performed in August 1974 and simultaneous renal transplant biopsy showed very minimal nephrocalcinosis. Ureteric stenosis and urine leakage from the ureterotomy necessitated transvesical reimplantation of the ureter 3 weeks later.

Post-operative plasma creatinine was 408.8 μmol/l, the plasma urea 1.6 mmol/l and GFR 60 ml/min. Serum calcium ranged between 2.35 mmol/l and 2.58 mmol/l, total serum protein 62 g/l and serum phosphate was normal. The alkaline phosphatase range for this period was 31 to 103 IU/l.

He has remained well with satisfactory transplant function and no evidence of recurrent calculi.

Surgical Technique

An extraperitoneal approach to the transplanted kidney, ureter or bladder was employed in each case. Access was gained through the original transplant wound (Cases 1 and 3), lower midline (Case 2) or a Pfannenstiel incision (Case 3). External drainage (Ragnall drains) was provided in all cases.

Retrieval of the calculus from the renal pelvis (Case 1) was effected through a vertical incision 3 cm above the pelvi-ureteric junction, after which closure was effected with continuous chromic catgut sutures.

In Case 2 the vesico-urethral calculus was removed through an anterior vesicotomy through which catheterisation and mechanical clearance of the transplanted ureter were also performed. The vesicotomy was closed in 2 layers with catgut and dexon and temporary urethral catheter drainage provided.

A fragmented ureteric calculus was extracted in Case 3 through a vertical ureterotomy followed by closure with interrupted dexon sutures around a T-tube drain. This was brought out through a stab incision in the anterior abdominal wall. Ureterolysis in this patient was accomplished by sharp dissection. Reimplantation of the ureter in a submucosal tunnel was carried out through an anterior vesicotomy which was closed in 2 layers with dexon sutures. Per urethral catheter drainage of both ureter and bladder was provided.

Discussion

The association of hypercalcaemia and urinary tract calculi is well documented.

In renal failure and after renal transplantation increased calcium is common (McPhaul *et al.*, 1964; Hume *et al.*, 1966; Schwartz *et al.*, 1970). Elevation may occur immediately after transplantation or be delayed for 6 months (Wilson *et al.*, 1965). It may be transient or last for several years (David *et al.*, 1973; Bigos *et al.*, 1976).

The cause of hypercalcaemia after renal transplantation is a matter for debate. Most attention has been given to secondary hyperparathyroidism for this is a frequent complication of chronic uraemia which lasts for a variable period after grafting (Castleman and Kibbee, 1963; Latimer *et al.*, 1970; Johnson *et al.*, 1971). The association with calculi in the transplanted kidney is also well recognised (Wilson *et al.*, 1965; Stevens *et al.*, 1969; Walsh, 1969; Starzl *et al.*, 1970; Rosenberg *et al.*, 1975; Leapman *et al.*, 1976). In such cases of secondary hyperparathyroidism, the characteristic radiological changes in bone may be absent and the biochemical changes may remain masked until revealed by low serum phosphate levels after transplantation (Alfrey *et al.*, 1968). Phosphate chelating agents, such as aluminium hydroxide, which may be used for prophylaxis against steroid induced gastrointestinal ulceration, can initiate such hypophosphataemia.

Other factors may contribute to hypercalcaemia. Dominguez *et al.* (1970) have suggested that it is related to improved renal function occurring after transplantation. Certainly, hypercalcaemia is more common in transplanted patients with a creatinine clearance greater than 60 ml/min (David *et al.*, 1973). Others believe that steroids used for immunosuppression may be important, whilst renal tubular acidosis and alteration of Vitamin D metabolism in the graft are possible aetiological factors. Steroids can cause skeletal decalcification and increased urinary clearance of phosphorus with hypophosphataemia. In renal tubular acidosis the urine is alkaline and this facilitates precipitation of calcium phosphate. In addition, hypercalcaemia may occur (Geis *et al.*, 1973) but the mechanism is still obscure. An increase of hydroxylated metabolites of Vitamin D has been reported in renal allografts and these may cause hypercalcaemia by enhancing absorption of calcium from the bowel (Leapman *et al.*, 1976).

Proponents of conservative treatment of hypercalcaemia following transplantation argue for administration of phosphate supplements, at least in the early stages. They believe that low serum calcium levels initiate hyperparathyroidism and hypercalcaemia. If this is true, parathyroidectomy should be reserved for resistant cases and those with evidence of metastatic calcification or secondary bone disease (Geis *et al.*, 1973).

Established secondary hyperparathyroidism demands parathyroidectomy. Indeed, Leapman advocates early surgery when secondary hyperparathyroidism and recurrent transplant calculi occur (Leapman *et al.*, 1976).

The surgical management of calculi and transplanted kidneys should follow the same principles which apply to untransplanted kidneys. Operative removal is indicated if obstruction or infection is present or if there is progressive enlargement of

Table 1 Summary of Case Reports of 3 Patients Developing Calculi in Their Allografts

Case	*Sex and age (years)*	*Donor details*	*Calculus type*	*Time of appearance of calculus after transplantation (months)*	*Treatment of calculus*	*Underlying cause and treatment*	*Present allograft status*
1	F 31	Live related	Calcium phosphate	21; 23	Pyelolithotomy	Hypercalcaemia Hyperparathyroidism Subtotal parathyroidectomy	Satisfactory Serum creatinine 190 μmol/l Follow-up period since transplant 6.5 years
2	M 39	Live related	Calcium phosphate	5; 8	Vesicolithotomy; ureteric clearance	Hypercalcaemia Hyperparathyroidism Subtotal parathyroidectomy	Satisfactory Serum creatinine 120 μmol/l Follow-up period since transplant 5 yr
3	M 39	Live related	Calcium phosphate	5	Ureterolithotomy	Ureterovesical stenosis; ureterolysis and re-implantation of ureter	Satisfactory Serum creatinine 220 μmol/l Follow-up period since transplant 2.5 yr

the stone. A higher incidence of post-operative complications would seem inevitable because of poorer healing and greater risks of infection due to long-term immunosuppression.

The collective requirements for development of a calculus or recurrent calculi in the renal allograft were present in 2 of our patients. One had recurrent urinary infections, renal tubular acidosis and secondary hyperparathyroidism with hypercalcaemia. Hypercalcaemia was probably most important since normal serum calcium which followed subtotal parathyroidectomy has been associated with no further calculi. Urine infection could be a contributory cause but repeated infections continuing after parathyroidectomy have not been accompanied by further urinary calculi.

Secondary hyperparathyroidism caused hypercalcaemia and recurrent calculi in a second case (Case 2). After parathyroidectomy the patient was normocalcaemic but vigorous administration of calcium supplement and Vitamin D induced hypercalcaemia and probably accounts for a further calculus at that time.

The third case had neither hypercalcaemia nor hyperparathyroidism and his calculus seemed to follow urinary infection and stagnation caused by stenosis of the ureterovesical anastomosis. A similar aetiology accounts for the formation of calcium in allograft ureters that have been implanted in ileal conduits (Rattiazzi *et al.*, 1975). Following restoration of patency and normal urinary drainage, further infection or stasis calculi have not been observed.

It is hoped that our experience will stimulate further awareness of this uncommon clinical problem. Prophylaxis rests with prompt recognition and treatment of hypercalcaemia and hyperparathyroidism or urinary stasis and stagnation. General urological principles dictate further management, although earlier intervention may be needed in these patients.

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The Diagnosis and Treatment of Lymphocoeles Associated with Renal Transplantation

A report of 6 cases and a review of the literature

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Summary—Six patients have developed a lymphocoele after renal transplantation, an incidence of 4%. A lymphocoele should be suspected in a patient who develops a rising creatinine with a pelvic mass or pressure effects on the pelvic veins 1 or more months after operation.

The diagnosis is confirmed by intravenous urography, venography and ultrasonography: the use of the latter as a diagnostic measure is recommended. Treatment is by marsupialisation into the peritoneum or external drainage with breakdown of all loculi. Aspiration is unsatisfactory.

A pelvic lymphocoele may result from an operation in which the pelvic lymphatic vessels are divided. Such collections of lymph were first described in the Japanese literature (Mori, 1955) in connection with pelvic lymph node dissection for carcinoma of the cervix and called lymphocysts because it was noted that they were thick walled, part being pelvic structures and the rest thickened peritoneum. The term lymphocoele was later substituted because they are probably not cysts within the strict definition of the word. Persisting collections of lymph following surgical division of lymphatics have been particularly reported in connection with operations in the groin (Fishback, 1947), repair of an abdominal aneurysm (Buonocorě *et al.*, 1965) and presacral neurectomy (Judd and Nix, 1949).

Lymphocoeles in association with renal allografts were first mentioned in 1968 by Hume and in 1969 by Inocencio and his colleagues. The importance of the presence of a lymphocoele is its effect on the surrounding structures; pressure on the iliac veins may cause leg swelling, pressure on the graft ureter may cause hydronephrosis and impaired renal function and the lymphocoele may even enlarge so much as to displace the urinary bladder, affecting the act of micturition. Lymphocoeles are usually sterile and only liable to become infected after surgical intervention.

Patients and Methods

In the Perth series of 156 transplants performed between 1967 and 1977, 6 patients developed lymphocoeles, an incidence of 4%.

Case 1

E.N., a 48-year-old woman with familial nephritis, received a renal allograft in March 1975, the graft being placed in the left iliac fossa. Two weeks after operation there was a short period of acute rejection which was treated successfully. However, 40 days postoperatively her left leg began to swell and a mass was felt on the left side of the pelvis on rectal examination. Ultrasonography confirmed the cystic nature of the mass (Fig. 1). Serum creatinine rose to 350 μmol/l, blood glucose was 13.8 mmol/l and blood pressure 130/80.

A venogram demonstrated nearly complete occlusion of the left common iliac vein by an extrinsic mass (Fig. 2) and an intravenous urogram indicated that the bladder was displaced to the right and also mild pelvicaliceal dilatation in the transplant kidney; 500 ml of clear fluid were drained externally at wound exploration from a lymphocoele. Seven weeks later the left leg was again swollen and creatinine elevated to 250 μmol/l and a marsupialisation of the lymphocoele was necessary; internal drainage was required again 4 months later because of rising creatinine and ureteric obstruction, after which she made an uneventful recovery.

Case 2

A.P., a 39-year-old man with chronic glomerulonephritis, had a second transplant in April 1975 (into the right iliac fossa), the first transplant having been

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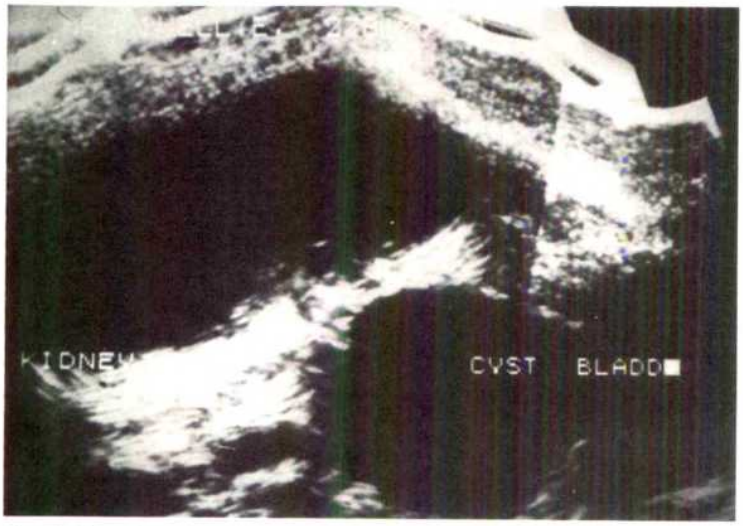


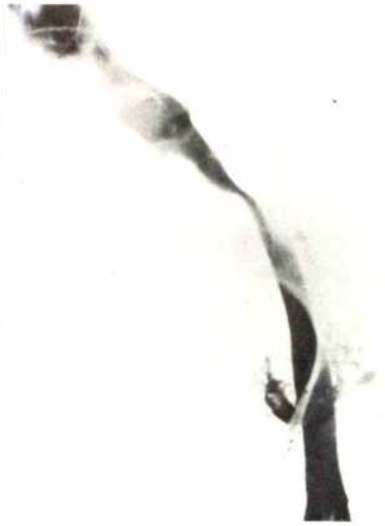


Fig. 1 Lymphocoele at lower pole of transplant kidney seen on ultrasound.

Fig. 2 Venogram showing compression of left common iliac vein.

rejected. Two weeks post-operatively his legs began to swell, this being more marked in the right leg; later he developed a small ulcer on this leg. He was at this time being treated with soluble insulin for steroid-induced diabetes. Creatinine was 410 μmol/1, blood pressure 170/80.

A venogram showed no evidence of venous obstruction, but a pyelogram demonstrated a dilated collecting system and deviation of the bladder to the left. At laparotomy 600 ml of clear fluid were drained internally into the peritoneum from a lymphocoele in the lateral pelvic wall. One month later the patient complained of difficulty in micturition relieved by massage over the transplanted kidney. The creatinine had risen to 250 μmol/1 and internal drainage of the lymphocoele was repeated, since which time he has had no further symptoms.

Case 3

J.R., a 57-year-old male, had his third renal transplant in February 1976, which was placed in the right iliac fossa and was successfully treated for acute rejection after 4 weeks.

Five months later his creatinine rose to 200 μmol/1 and he had mild ankle swelling. An intravenous pyelogram was normal, but an ultrasound scan showed a sonolucent round cystic area below the inferior pole of the transplanted kidney. No surgical treatment was deemed necessary and the creatinine fell to normal after treatment for rejection. Later ultrasound scans no longer showed the collection of fluid.

Case 4

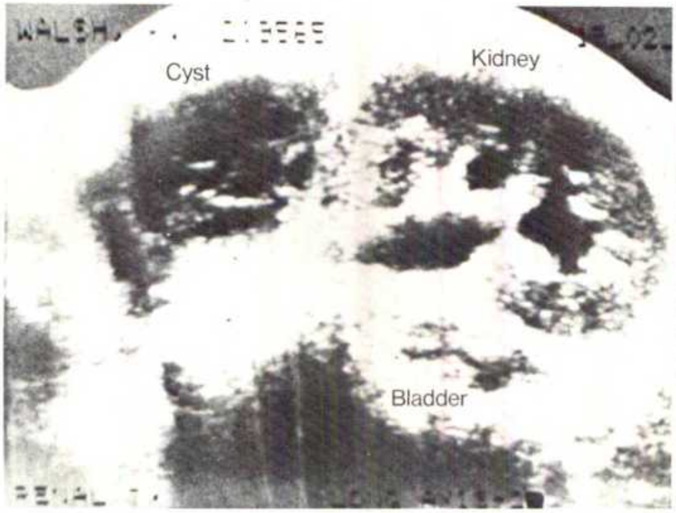
K.W., a 20-year-old man with obstructive nephropathy consequent on congenital urethral valves, had a renal transplant placed in the left iliac fossa in August 1975. Apart from requiring haemodialysis in the first post-operative week, his progress was uneventful for 3 months, when an enlarging mass was found in the left inguinal region. The serum creatinine was 410 μmol/1 and a pyelogram showed slight distension of the pelvicaliceal system and displacement of the bladder to the right; as the creatinine fell, no surgery was performed. His left leg became swollen 12 months after transplantation, and an ultrasound scan showed a large fluid-filled mass on the left side of the pelvis (Fig. 3). This was drained internally but the swelling recurred 4 months later when he complained of difficulty in emptying his bladder; a pyelogram showed moderate hydronephrosis of the kidney and the bladder displaced to the right (Fig. 4). The lymphocoele was drained externally and he has had no recurrence now 6 months later.

Case 5

D.S., a 50-year-old man with a 3 year history of glomerulonephritis, was transplanted in July 1976 with a kidney placed in the right iliac fossa. Twelve days later he developed a scrotal swelling and after a month his right leg became swollen and oedematous. There was no abnormal mass palpable apart from the transplant kidney but a venogram showed compression of the right common iliac vein with the bladder displaced to the left. Serum creatinine was 140 μmol/1, blood sugar 15.7 mmol/1. In October 1976 a retroperitoneal lymphocoele was drained into the peritoneum and his subsequent progress has been unremarkable.

Case 6

B.D., a 47-year-old woman with glomerulonephritis, received a renal allograft to the left iliac fossa in June



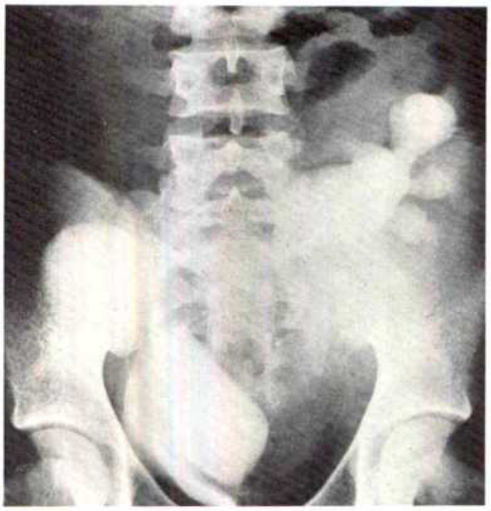


Fig. 3 Ultrasound showing lymphocoele at lower pole of transplant kidney.

Fig. 4 Intravenous urogram showing dilatation of collecting system of graft kidney and compression of the bladder.

1975. Unfortunately it was rejected and a transplant nephrectomy performed 1 month later. Three months later she became aware of a mass in the left inguinal region which fluctuated in size; there were no other symptoms or signs and no radiological abnormality. In November 1975 an extraperitoneal lymphocoele containing 500 ml of clear fluid was drained and marsupialised and she made a good recovery.

Discussion

The development of a lymphocoele after renal transplantation can now be fairly readily recognised but it has to be distinguished from other fluid collections—firstly from a collection of blood or serum, and secondly from urine collections resulting from leaks from the bladder incision, a sloughing ureter or localised necrosis of the transplanted kidney. In practice, a urinary leak nearly always occurs within 3 weeks of transplantation, whereas lymphocoeles present later. In our series the 2 earliest were recognised after 1 month, 2 more at 3 months and 2 at 5 months, of which 1 recurred a year later. A fluid collection which drains spontaneously from a transplant wound in the first 2 weeks is not rare, but whether this is significant in relationship to later formation of lymphocoeles is uncertain.

The first suspicion of the presence of a lymphocoele may be a rising serum creatinine with mild hydronephrosis developing in the transplanted kidney without any other signs of rejection. The diagnosis is sometimes made more difficult because the back pressure effects on the kidney may cause not only an elevation of serum creatinine and proteinuria but also swelling of the graft with some tenderness and mild fever. This simulates a rejection episode which may occur concurrently. Braun *et al.* (1974) suggested that non-pitting oedema of the tissues overlying the allograft or swelling in the ipsilateral lower abdominal, suprapubic, genital and thigh areas are to be seen in all patients with lymphocoeles but we have not found this a great diagnostic help. A palpable suprapubic swelling occurred in 41 of 59 patients reviewed (Table 1) and is of importance, though this may prove to be an overfull bladder rather than the lymphocoele. Pressure effects on the main iliac veins are common (4 out of 6 in our series) with the development of ipsilateral leg oedema. The possibility of an ilio-femoral thrombophlebitis being present usually results in venography being carried out and this shows a characteristic external pressure effect on the large veins. Lymphocoeles are not always palpable, for they usually lie posteromedially to the kidney over the iliac vessels. As they enlarge they bulge forward and the transplanted ureter may lie in the wall. The position of the ureter may be difficult to determine and injuries to it during surgical drainage have been reported (Schweizer *et al.*, 1972). In 1 patient in our series the bladder was so displaced by the

Table 1 Previously Reported Findings in 53 Patients* +6 R.P.H. Patients

	Total 53	*Total 6*
Abdominal mass	38	3
Ipsilateral leg oedema	31	4
Hypertension	14	-
Drainage from incision	10	-
Fever	10	-
Previous urinary tract infection	12	-
Reduced urine volume	8	1
Thrombophlebitis	2	-
Frequency	6	1
Hyperglycaemia	-	3
Leg ulcer	-	1
↑ Serum Creatinine	36	5

* Baglin *et al.*, 1972; Braun *et al.*, 1974; Curran *et al.*, 1976; Hume, 1968; Inocencio *et al.*, 1969; Kiser *et al.*, 1971; Koehler, 1972; Koehler and Kyaw, 1972; Lorimer *et al.*, 1975; Madura *et al.*, 1970; Meyers *et al.*, 1975; O'Donoghue *et al.*, 1971; Pillay *et al.*, 1971; Schweizer *et al.*, 1972; Smellie *et al.*, 1968; Starzl *et al.*, 1970; Zincke *et al.*, 1975.

Table 2 Initial Treatment

	†Previously Reported—72	*R.P.H.—6*
Nil	7 (4)	1
Aspiration	19 (16)	-
External drainage	31* (5)	1 (1)
Internal drainage	8 (1)	4 (2)
Spontaneous drainage	4 (2)	-
Graft nephrectomy	1	-
Ureteric catheter	2	-
Lymphatic ligation	-	-

(Recurrence rate in brackets)—see Table 3.

* Three died following external drainage.

† Baglin *et al.*, 1972; Braun *et al.*, 1974; Buckingham *et al.*, 1976; Curran *et al.*, 1976; Hume, 1968; Inocencio *et al.*, 1969; Kiser *et al.*, 1971; Koehler, 1972; Koehler and Kyaw, 1972; Lipschultz *et al.*, 1976; Lorimer *et al.*, 1975; Madura *et al.*, 1970; McDonald and Libertino, 1976; Meyers *et al.*, 1975; Moreau *et al.*, 1973; O'Donoghue *et al.*, 1971; Pillay *et al.*, 1971; Schweizer *et al.*, 1972; Smellie *et al.*, 1968; Starzl *et al.*, 1970; Zincke *et al.*, 1975.

lymphocoele that urinary difficulty and retention of urine were experienced. A review of the literature (Table 1) shows a substantially similar pattern of symptoms and signs in other series with a rising creatinine, an abdominal mass and leg oedema as the commonest findings. A deterioration in renal function expressed by a rising serum creatinine occurred in 41 out of 59 cases. An intravenous urogram may show either bladder displacement, an external impression on the ureter or developing hydronephrosis. Five of our 6 cases showed this abnormality.

Venography was performed invariably when there was swelling of the limb and this showed indentation of the common and external iliac veins from without. In our series, 3 of the 4 patients so investigated demonstrated such a lesion compared with 59% from the literature. Possibly the most significant advance in detection of a lymphocoele is the use of B-mode ultrasonography, a method we have employed successfully in all the cases since the apparatus became available to us. We have found this to be a most valuable aid and recommend it as a non-invasive technique which appears to be reliable both from our own experience and that of others (Curran *et al.*, 1976; Lipschultz *et al.*, 1976; McDonald and Libertino, 1976). It should be noted that the ultrasound shows up the partitions which are not infrequent in these structures and which probably account for difficulties experienced in surgical drainage.

Pedal lymphangiography demonstrates that the source of the lymph is for the most part from divided pelvic lymphatics (Koehler, 1972), though there may be lymph seepage from the graft. Lymphocoeles can develop after a rejected graft has been removed (Braun *et al.*, 1974). As a diagnostic tool lymphangiography has a definite morbidity and for this reason has not been practised as a routine diagnostic method.

There is evidence from other surgical operations that the more extensive the removal of lymphatic tissue the more likely it is that a lymphatic fistula will develop and persist and there is no reason to suppose that this does not apply to a renal transplant. Prophylaxis by minimal interference with iliac lymphatics would seem to be important and particularly ligation of any vessels that interfere with graft placement rather than their diathermy division.

Table 3 Treatment of Recurrences

	Previously Reported—28	*R.P.H.—3*
Nil	6	-
Aspiration	2	-
External drainage	13	1
Internal drainage	6	2
Spontaneous drainage	-	-
Graft nephrectomy	-	-
Ureteric catheter	-	-
Lymphatic ligation	1	-

It has been shown that aspiration of a lymphocoele is inadequate treatment and results either in infection, recurrence or both (O'Donoghue *et al.*, 1971). Drainage is therefore required either to the surface or by marsupialisation through a very large hole into the peritoneum. A review of our own work and that of others shows, however, that irrespective of the method of drainage, recurrences occur (Tables 2 and 3). These may be due to failure to drain a loculus of the lymphocoele which is often partitioned, rather than a reforming of the drained sac, though the latter remains a possibility. The advantage of marsupialisation is that infection is less likely but it increases the risk of damage to the transplanted ureter. We have preferred this technique to external drainage, though we have resorted to the latter if recurrence occurred. Direct ligation of the lymphatic fistula, though theoretically attractive, has not yet been tried in these cases. It would probably be difficult to achieve technically.

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Ureteric Involvement with Abdominal Aortic Aneurysm

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Summary—The clinical presentations of 3 patients found to have an abdominal aortic aneurysm with ureteric involvement have been described. The world literature concerning this problem and methods of surgical treatment have been reviewed.

The importance of medial displacement of the ureters as an early diagnostic sign indicating the presence of an abdominal aortic aneurysm is again emphasised. The possibility of a relatively benign course for the aneurysm should be considered in patients with renal or cardiorespiratory complications. In such cases, treatment of the ureteric involvement alone is justified.

Aneurysms of the abdominal aorta may masquerade as disease of the genitourinary tract in their mode of clinical presentation. This fact is well recognised following the accounts of Uhle (1941) and Lazarus and Marks (1944). However, ureteric obstruction associated with aneurysm of the aorta is rare. Two cases are presented which illustrate early involvement of the ureters by aortic aneurysm, and a third case is described in which the ureteric obstruction led to nephrectomy. A careful review of the literature has revealed 26 cases which have been treated by surgery.

Both partial ureteric obstruction and medial ureteric displacement give the urologist the opportunity to diagnose aortic aneurysm at an early stage. The technique of dynamic intravenous radionuclide angiography (angioscan) is recommended as a simple screening aid when aortic aneurysm is suspected. The management of ureteric obstruction from this cause is discussed in the light of reported experience.

Case Reports

Case 1. A 63-year-old man, who had been an in-patient for a considerable period with a depressive psychosis, developed severe abdominal pain in October 1975. He had complained of backache for many years and previously had been noted to have a chronic duodenal ulcer and Paget's disease of the third lumbar vertebra.

On clinical examination he was shocked, confused and mentally retarded. On palpation of the abdomen, generalised rigidity and rebound tenderness were noted. At laparotomy, a fusiform aneurysm of the abdominal aorta was found. This extended from below the renal

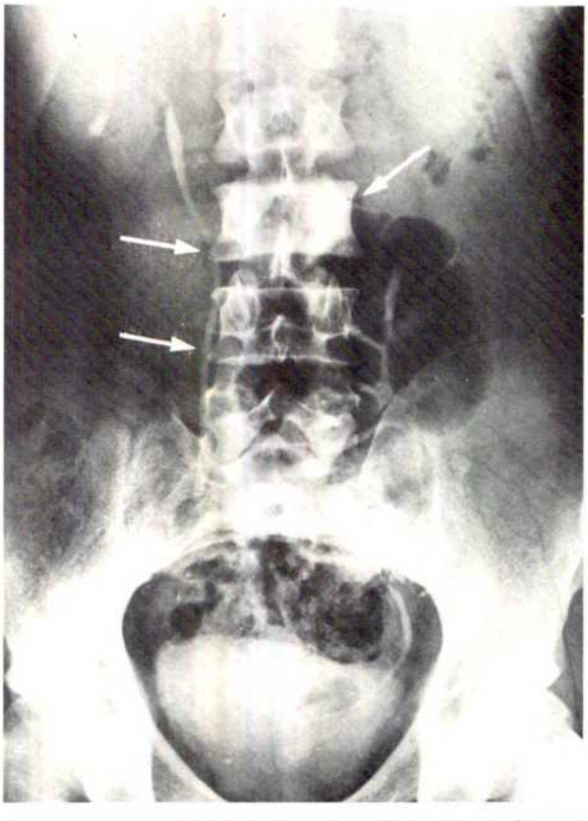

Fig. 1 Showing medial displacement of the ureters 8 years prior to rupture of aneurysm and Paget's disease of L3 vertebra.

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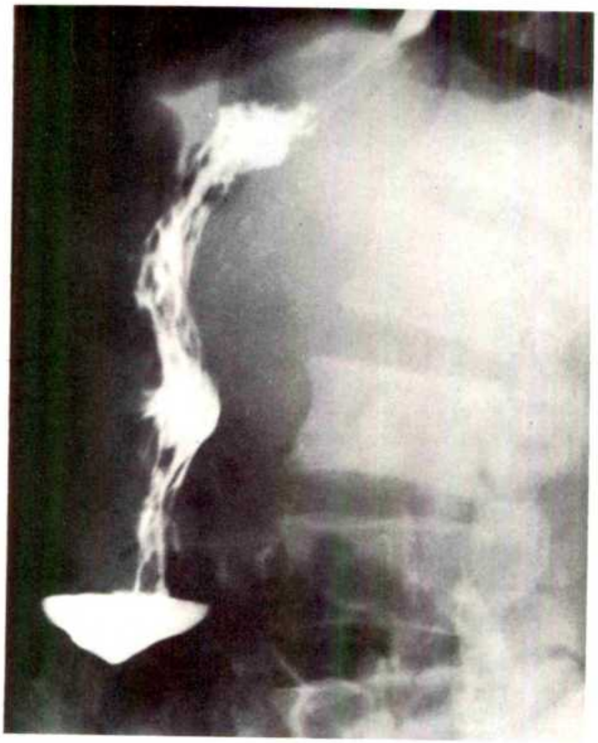

Fig. 2 Aortic aneurysm causing anterior displacement of stomach.

arteries to the aortic bifurcation. Leakage had occurred into the retroperitoneal tissues. In view of his past medical history, no further procedure was undertaken and he died on the second post-operative day.

A retrospective review of his X-ray investigations revealed medial displacement of the ureters on an IVU taken 8 years previously (Fig. 1). A lateral view of his barium meal demonstrated the aneurysm (Fig. 2).

Case 2. An 80-year-old man was admitted in 1975 with left-sided abdominal pain. In the past, he had suffered from long-standing congestive cardiac failure and in 1966 a small abdominal aortic aneurysm had been diagnosed on clinical examination. In view of his cardiac state, no further investigations had been performed.

On examination he was not shocked. His blood pressure was 120/80 mm Hg, his jugular venous pressure was elevated at 5 cm, and he had atrial fibrillation. An easily palpable, pulsatile and expansile mass was noted in the epigastrium. His symptoms quickly subsided without specific treatment. An IVU revealed a normal right kidney. The left pelvicaliceal system was dilated, the upper ureter being displaced medially and partially obstructed (Fig. 3). This was attributed to extrinsic compression by peri-aneurysmal fibrosis. He was discharged without undergoing further treatment or investigation and he remains well.

Case 3. A 77-year-old man presented in 1972 with a 36 h history of epigastric pain radiating through to the back. He had recently suffered an episode of painless haematuria. In the past, a fractured neck of the right femur had been treated by internal fixation. No abnormality was found on general examination.

An IVU revealed a non-functioning right kidney (Fig. 4). In addition, some calcification was noted to the right of the second lumbar vertebra. Cystoscopy was performed and a papilliferous tumour was found, overlying the right ureteric orifice (transitional cell carcinoma, with no evidence of invasion, Stage I). This was resected and fulgurated. Follow-up cystoscopic examinations revealed no recurrence of the tumour, but a retrograde ureterogram failed to outline the ureter. Because of the possibility of further tumour being present in the right kidney and ureter, a nephroureterectomy was performed.

During this procedure, a hydronephrotic kidney was mobilised and the ureter was found to be dilated in its upper half, but collapsed below a point where it was caught in an area of retroperitoneal fibrosis. This surrounded a small fusiform aortic aneurysm. The peritoneum was opened and the left ureter was found to be

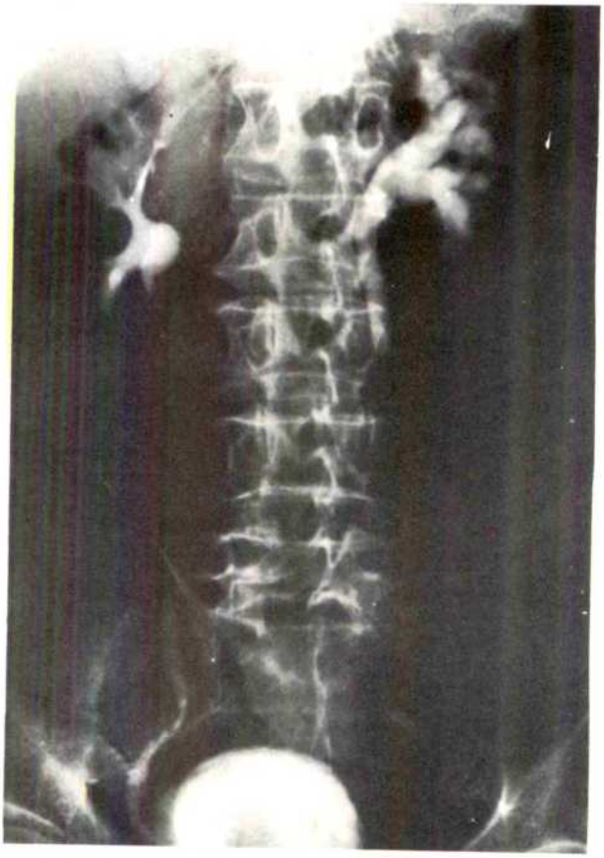

Fig. 3 Medial deviation and partial obstruction of left ureter.

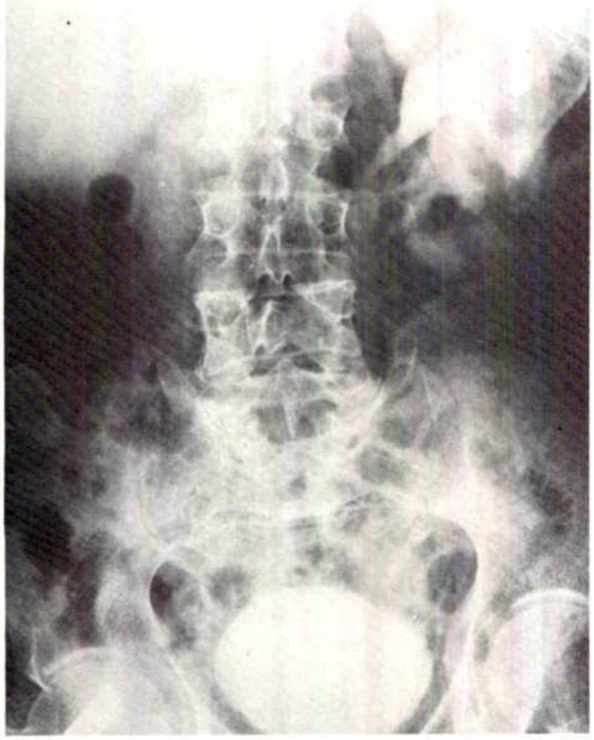

Fig. 4 Non-functioning right kidney secondary to peri-aneurysmal fibrosis obstructing the ureter.

free of any similar process. The operation was completed and recovery was uneventful. The opinion of a vascular surgeon was sought and he advised that no further surgery be performed on the aneurysm, unless symptoms arose or the left ureter became involved.

Subsequently a dynamic intravenous Tc^{99m} pertechnetate angiogram was performed by giving 10 mCi of isotope as a bolus injection into an antecubital vein. The data were collected using a Searle LFOV Gamma camera, connected to a PDP 11/45 computer system. This clearly demonstrated the aneurysm (Fig. 5). The patient died of congestive cardiac failure 5 years after his surgery, the aneurysm remaining clinically unchanged.

Discussion

In 1935, James first reported the autopsy of a woman who died with uraemia and was known to have an aortic aneurysm. He found "renal atrophy" due to a combination of pressure on the renal arteries and the ureters. Renal ischaemia and uraemia were later noted to be associated with a saccular aortic aneurysm (Howland and Sprofkin, 1943) and with a dissecting aneurysm (Halprin, 1943). Goodwin and Shumacker (1947) first reported urinary tract obstruction associated with an aneurysm of the hypogastric artery, and obstructive uropathy secondary to an abdominal aortic aneurysm was described by Shumacker and Garrett in 1955. A careful review of the literature has revealed 7 cases of abdominal aortic aneurysm presenting with anuria (Table 1); 12 cases presenting with partial bilateral ureteric obstruction (Table 2); and 7 cases presenting with unilateral ureteric obstruction (Table 3).

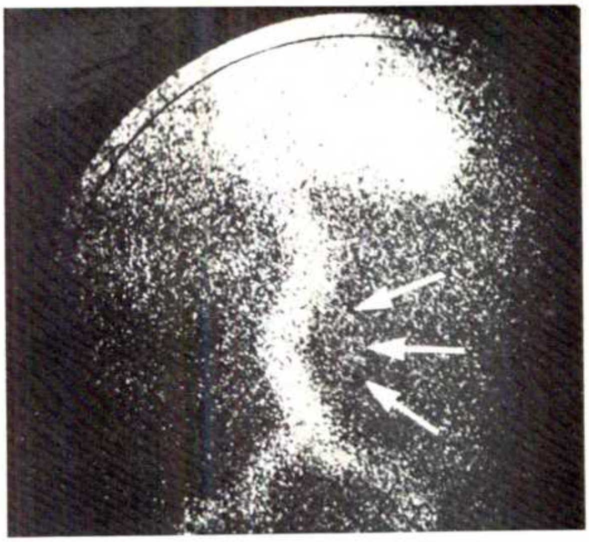

Fig. 5 Dynamic intravenous radionuclide angioscan revealing aortic aneurysm of Case 3.

These reported cases may not be an accurate reflection of the true incidence of ureteric involvement with abdominal aortic aneurysm. Culp and Bernatz (1961) found that 10% of 400 cases with aneurysm of the abdominal aorta had symptoms suggestive of a urological disorder. Most reported cases have been mistaken for hydronephrosis (Duchanoff, 1934), renal calculi, ureteric calculi or perinephric abscess (Lazarus and Marks, 1944). Abnormal excretory urograms have been detected in 25% of cases prior to resection of abdominal aortic aneurysm (Labardini and Ratliff, 1967). This usually takes the form of medial displacement of the ureter. Peck *et al.* (1973) found "traction" displacement of the ureter in 71% of 45 cases with abdominal aortic aneurysm. Displacement was considered to be significant if the ureter passed over a vertebral body or close to the lateral cortex. They propose that this is the earliest diagnostic clue to the presence of an aneurysm. Certainly, in our first case, medial displacement of the ureters had been

Table 1 Seven Cases Presenting with Anuria, due to Ureteric Obstruction caused by Abdominal Aortic Aneurysm

Author		*Sex*	*Age*	*Treatment*		*Outcome*	*Follow-up period*
				Aneurysm	*Ureters*		
Shumacker and Garrett	1955	M	60	Resected	Ureterolysis	Survived	4 months
De Weerd *et al.*	1955	M	45	Laparotomy: none	Bilateral nephrostomy	Survived	15 months
Jellinek	1956	M	56	None	Bilateral nephrostomy	Died	7 weeks
Pearlman and Mackey	1960	M	62	Resected	Left nephrostomy	Died	26 days
Culp and Bernatz	1961	?	?	Resected	Ureterolysis	Survived	No details
Spittell and Hunt	1966	M	69	Resected	Ureterolysis	Survived	4 months
Friedel *et al.*	1973	M	67	Laparotomy: none	Peritoneal dialysis Bilateral nephrostomy	Survived	18 months

present for at least 8 years prior to rupture of the aneurysm. However, medial ureteric displacement can simply be a normal variant (Saldino and Palubinskas, 1972), or may occur in idiopathic retroperitoneal fibrosis (Ormond, 1948), retrocaval ureter, retroperitoneal tumours (Ney and Friedenberg, 1966), or with pelvic lipomatosis (Moss *et al.*, 1972).

Significant ureteric obstruction caused by extrinsic compression was treated surgically by ureterolysis by Albarran in 1905. This technique has been widely used to release the ureter from peri-aneurysmal fibrosis. Some patients in the early series survived following the creation of a nephrostomy either as a permanent or temporary measure (Tables 1, 2 and 3). Following advances in the techniques of arterial surgery, resection of the aneurysm has been undertaken with homograft or prosthetic aortic replacement, combined with ureterolysis. Unfortunately, the follow-up period of many of the reported cases is inadequate for an accurate comparison of the various techniques to be made. The causes of the deaths in the reported series are shown in Table 4.

In principle, the ideal procedure would appear to be resection of the aneurysm, insertion of a vascular prosthesis and ureterolysis. However, in an elderly patient with associated renal impairment and cardiac or respiratory problems, simple ureterolysis should be considered (Abercrombie and Hendry, 1971; Abbott *et al.*, 1973). The presence of dense peri-aneurysmal fibrosis appears to protect against the likelihood of rupture of the aneurysm. One of the cases reported here (Case 3) survived a period of 5 years after ureterolysis and nephroureterectomy.

Table 2 Twelve Cases Presenting with Bilateral Ureteric Obstruction caused by Abdominal Aortic Aneurysm

Author		*Sex*	*Age*	*Treatment*		*Outcome*	*Follow-up period*
				Aneurysm	*Ureters*		
Schloss and Kaplan	1953	M	64	Packed with wire	Ureterolysis	Survived	6 months
Crane	1958	M	60	None	Ureterolysis	Died	2 months
Crane	1958	M	53	Resected	Ureterolysis	Survived	11 months
Szilagyi *et al.*	1966	M	60	Resected	Ureterolysis	Survived	?
Charnock *et al.*	1961	M	63	Resected	Ureterolysis	Died	18 months
Kaufman	1962	M	58	None	Ureterolysis	Survived	2 months
Pallette *et al.*	1967	M	61	Resected	None	Died	14 days
Labardini and Ratliff	1967	M	60	Resected	Ureterolysis	Survived	No details
Wagenknecht and Madsen	1970	M	74	None	Ureterolysis	Survived	5 months
Wagenknecht and Madsen	1970	M	65	None	Ureterolysis	Survived	4 months
Cerny and Scott	1971	M	60	Resected	Ureterolysis	Survived	No details
Abbott *et al.*	1973	M	64	None	Ureterolysis	Survived	6 weeks

Table 3 Seven Cases of Unilateral Obstruction caused by Abdominal Aortic Aneurysm

Author		*Sex*	*Age*	*Treatment*			*Outcome*	*Follow-up period*
				Aneurysm	*Ureter*	*Side*		
Lazarus and Marks	1944	F	58	None	None	Left	Survived	2 years
Szilagyi *et al.*	1966	?	?	Resected	Nephrectomy	?	?	No details
Albers and Bettaglio	1961	M	50	Delayed resection	Ureterolysis	Left	Survived	2 months
Cottler and Immergut	1961	M	54	None	Ureterolysis and Nephrostomy	Left (Solitary)	Died	2 years
Beal	1966	M	48	Resected	Ureterolysis	Left	Survived	2 months
Abercrombie and Hendry	1971	M	65	None	Ureterolysis	Right (Solitary)	Survived	1 year
Boontje *et al.*	1974	M	57	Resected	Ureterolysis	Left	Survived	1 year

We recommend the technique of dynamic intravenous radionuclide angiography (using Tc^{99m} pertechnetate) as a simple, rapid and safe method of screening patients in whom an abdominal aortic aneurysm is suspected (Bergan *et al.*, 1974). The technique is of special benefit in the elderly patient with impairment of cardiac or renal function. In such cases, conventional contrast angiography is contra-indicated. We believe the method supplies more useful information than ultrasound scanning of the abdomen. The patency of the peripheral vessels can be seen, and an assessment of renal perfusion can be made on the computerised data.

Table 4 Cause of Death in 6 Cases Treated Surgically for Ureteric Obstruction Associated with Aortic Aneurysm

Aneurysm untreated: 11 cases	*Aneurysm treated: 15 cases*
1. Renal sepsis after 7 weeks.	1. Haemorrhage from homograft after 2 weeks.
2. Ruptured aneurysm after 2 months.	2. Intestinal ischaemia after 1 month.
3. Ruptured aneurysm after 2 years.	3. Haemorrhage from aorto-duodenal fistula after 18 months.

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The Influence of Early Post-Operative Intravenous Nutrition upon Recovery after Total Cystectomy

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Summary—A retrospective review was made of the effect of early post-operative total parenteral nutrition on recovery from total cystectomy with formation of an ileal conduit. No difference in mortality or time spent in hospital after operation was noted between 2 groups receiving either total parenteral nutrition or isotonic dextrose-saline solutions.

Total cystectomy with urinary diversion by formation of an ileal conduit is associated with considerable mortality and morbidity (Sarma, 1969; Whitmore, 1973). In many centres, including our own, this operation is therefore reserved largely for cases with either local recurrence of tumour or haemorrhage after radiotherapy. Many of the complications are related to infection or failure of wound healing which may be delayed after previous irradiation.

The association between depletion of protein reserves and both susceptibility to infection and impaired healing has long been recognised (Studley, 1936). Protein depletion may become marked after cystectomy as a result of increased protein catabolism after operation and near starvation. In the event of post-operative complications such loss may be extreme, although nitrogen balance can be restored and weight gain obtained by intravenous feeding (Lee, 1975). The success of intravenous feeding in such cases has led to recommendations for its use from as early as the third post-operative day in patients who have not resumed oral feeding, in the hope of limiting nitrogen loss and reducing complications (Irving and Rushman, 1971; Lee, 1975). Recent reports by Bistrian *et al.* (1974) and Hill *et al.* (1977) of a high incidence of protein depletion in surgical patients, particularly 1 week after operation, may support this view.

In 1974 we adopted a policy of routine intravenous feeding after total cystectomy because of prolonged ileus and the high complication rate of the operation. It is not clear what degree of protein loss is critical. Parenteral nutrition itself has a significant complication rate (Ryan *et al.*, 1974). We therefore present a review of this change of policy.

Most of the risks associated with parenteral nutrition arise from the accompanying use of a central venous catheter. Blackburn *et al.* (1973) reported that infusion of an isotonic amino acid solution via peripheral venous cannulae markedly reduced nitrogen loss. We have therefore assessed nitrogen balance after cystectomy both during total parenteral nutrition and during infusion of a hypocaloric isotonic amino acid solution.

Methods

Case notes on all 71 patients who had undergone total cystectomy with formation of an ileal conduit between January 1970 and December 1976 were reviewed. Pathological specimens from these patients were re-examined and graded according to the IUCC Classification.

Total cystectomy was performed with removal of adjacent viscera when involved by tumour. Fifty-five patients received radiotherapy, usually 6000 Rad from a linear accelerator, though 7 had had a cystotomy and insertion of gold grains.

Before 1974 post-operative fluid and electrolyte balance was maintained with isotonic glucose and saline solutions yielding approximately 100 g glucose (400 cal) daily. From 1974, patients received full parenteral nutrition through central venous catheters usually inserted by experienced anaesthetic staff. Subsequently patients were

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cared for on general surgical wards. Various feeding regimes were used but most often these were composed of Vamin-Glucose* and Intralipid* or Aminoplex 5†.

Eleven of these patients and 6 operated upon subsequently were studied prospectively in respect of nitrogen balance. The 17 patients were randomly allocated into 3 groups. The first group received Vamin-Glucose and Intralipid 10% (35 non-protein cal/kg body weight/day and 0.21 g nitrogen/kg body weight/day), the second an equicaloric, equinitrogenous amount of Aminoplex 5 and the third 3.5% Synthamin‡ amino acid solution, providing 6 protein cal and 0.24 g nitrogen/kg body weight/day. All solutions provided electrolytes and about 3 litres water daily for a 70 kg patient. Nitrogen excretion was estimated on the third and seventh post-operative day from the urea content of urine and drainage specimens, with allowances for changes in blood urea as described by Lee (1974), and comparisons were made using Student's 't' test. We have recently validated the relationship between urine urea and total nitrogen content in post-operative patients (Foster *et al.*, in preparation).

Results

Thirty-eight patients received glucose-saline after operation and 33 received full parenteral nutrition. The latter group included 2 patients who were treated with the isotonic amino acid solution and were discharged on the thirteenth and eighteenth post-operative days after an uneventful recovery. The characteristics of the patients were similar (Table 1). Three patients were uraemic with blood ureas of 24, 28 and 30 mmol/l due to bilateral ureteric obstruction.

These 3 patients apart, there were no severe disturbances in blood urea and electrolytes after operation in either group except for an occasional marked rise in blood urea in patients developing complications.

Table 2 shows the outcome of operation in the 2 groups. Complete wound dehiscence occurred once in each group. The time spent in hospital after operation was similar in each group. Six patients in each group died in hospital. Three deaths occurred in the first week in each group and appeared to be related to the general medical condition of the patient or failure of technique. Later deaths were all due to infection and breakdown of anastomoses.

No metabolic complications of intravenous feeding were recorded. One patient died after developing a tension pneumothorax 3 days after the insertion of a subclavian venous catheter. Another patient receiving intravenous feeding died from septicaemia due to *Staphylococcus aureus* which developed after a prolonged intra-abdominal infection. The organism was cultured from both blood and catheter tip. Two non-fatal complications of central venous cannulae were

Table 1 Details of 71 Patients Undergoing Total Cystectomy between 1970 and 1976

	Glucose-saline post-operative	*IV feeding post-operative*		*Glucose-saline post-operative*	*IV feeding post-operative*
No.	38	33	No.	38	33
Male : female ratio	27 : 11	25 : 8	*Stage**		
Mean age	63	65	T_0	1	0
Previous radiotherapy	29	26	T_1	5	3
Mean plasma urea ± SEM			T_2	6	6
(excluding uraemic subjects)	5.4 ± 0.4	6.2 ± 0.4	T_3	16	18
No. uraemic patients			T_4	8	6
(plasma urea > 12 mmol/l)	1	2	P_0	6	2
Main Indication			P_1	9	15
Primary procedure	2	2	P_2	5	4
Local recurrence	18	15	P_3	16	11
Palliation	2	0	*Cell Type**		
Haemorrhage	4	3	Transitional	36	32
Small bladder	3	4	Squamous	2	1
Bilateral ureteric obstruction	4	3	Adenocarcinoma	1	0
Other	5	6			

* Where recorded.

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* KabiVitrum † Geistlich ‡ Travenol Laboratories

Table 2 Influence of Early Intravenous Feeding upon Recovery after Total Cystectomy

	Glucose-saline post-operative	*Total intravenous feeding post-operative*
Number of patients	38	33
Complete wound dehiscence	1	1
Mean time in hospital after operation (days)	23	21
(Range)	(13-43)	(11-45)
Hospital deaths		
1. Early	3 { Myocardial infarct Pulmonary embolism Bowel infarct	3 { Myocardial infarct Tension pneumothorax Synergistic gangrene of abdominal wall
2. Late (infection)	3	3
Total	6	6
Deaths* from metastases by 1 year post-operative	8/32	4/16

* After operations before May 1976 allowing follow-up for 1 year.

recorded, namely 1 case of hydrothorax and 1 axillary vein thrombosis.

The details of patients and results of the nitrogen balance study are shown in Table 3. On the third day, nitrogen balance was identical in both intravenous feeding groups. Since relatively few patients remained on intravenous feeding on the seventh day, the mean nitrogen balance for all total intravenous feeding is compared with that of isotonic amino acid infusion on that day. There was no significant difference in the estimated nitrogen balance (which excludes minor cutaneous losses) on either day, between those receiving conventional parenteral nutrition or the 3.5% amino acid solution.

One patient who received the 3.5% amino acid solution died after suffering a complete wound dehiscence; the remainder recovered satisfactorily.

Discussion

This review failed to show any clear benefit from a policy of routine administration of parenteral nutrition after total cystectomy. Since this study was retrospective it is not possible to evaluate accurately any effect upon minor wound or chest infections. We were not able to ensure complete similarity of treatment of our patients, but both groups were similar in respect of age, sex and indications for operation. Nevertheless, our overall finding accords with those of 2 prospective randomised trials of the value of total parenteral

Table 3 Details of and Nitrogen Balance in Patients Receiving Intravenous Feeding or Isotonic Amino Acid Solution

	Aminoplex 5	*Vamin-glucose and Intralipid 10%*	*3.5% Synthamin amino acid*
Number studied	6	6	5
Mean age (years) (range)	66 (51-84)	62 (52-72)	64 (41-83)
Mean weight (kg)	64	66	67
Mean weight as per cent of ideal body weight* (range)	104 (87-126)	102 (84-127)	113 (86-147)
Mean pre-operative plasma urea (mmol/l) (range)	7.5 (5.5-11.5)	6.8 (4.5-10.0)	7.5 (5.5-9.4)
Estimated nitrogen balance			
Day 3 (mean + SEM, g/kg/day)	−0.07 ± 0.01	−0.07 ± 0.01	−0.10 ± 0.04
Day 7 (mean ± SEM, g/kg/day)	+0.01±0.04 (n = 5)		−0.05 ± 0.05 (n = 4)

* Derived from data of Metropolitan Life Insurance Tables, Chicago, 1959.

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nutrition in the routine support of patients after cardiac (Abel *et al.*, 1976) and gastro-intestinal surgery (Holter *et al.*, 1976).

Assessment of the efficacy of parenteral nutrition depends on the criteria chosen but we believe our criteria are important both to the patient and economically. The time spent in hospital after operation may be the more sensitive measure of satisfactory recovery. During the period covered by this study we have not only gained more experience in the technique of total cystectomy but also adopted a more aggressive approach to the early discharge of patients. Both these factors may have shortened the time spent in hospital in the latter half of the study, but no significant difference was seen between the 2 groups. The overall mortality was 17% and is largely related to the age and infirmity of many of our patients. It is, however, within the range of up to 26% reviewed by Sarma (1969). Whitmore (1973) suggested that a mortality rate of 10% was to be expected after elective total cystectomy. Few of the cases reported here could be regarded as elective.

Improved results from full intravenous feeding might be expected when patients are cared for in specialist nutritional units rather than general surgical wards. However, it appears that routine post-operative parenteral nutrition does not markedly decrease the likelihood of complications after major operations. Both Abel *et al.* (1976) and Holter *et al.* (1976) reported that malnourished patients are more likely to suffer complications and further studies on our unit (Kammerling *et al.*, 1978) have confirmed this. Possibly the period of post-operative intravenous feeding given was too short or too late to repair the nutritional deficits associated with susceptibility to complications after surgery. When pre-operative parenteral nutrition was given before surgery for upper gastro-intestinal neoplasms, Williams *et al.* (1976) reported a reduction in mortality and wound infection. More information is required on methods to predict those patients in whom pre-operative nutritional support might reduce the incidence of complications.

In assessing nitrogen balance we chose 2 widely-used total parenteral nutrition regimes which may not be ideal. There may be a risk of lactic acidosis when sorbitol and ethanol are infused concurrently, as in Aminoplex 5 (Alberti and Nattrass, 1977). We therefore limited the amount of sorbitol infused (0.22 g/kg/h), thus providing less calories (35 cal/kg/day) than Spanier and Shizgal (1977) recommend for seriously ill patients. However, nitrogen balance was achieved by the seventh post-operative day as patients recovered from the catabolic stress of operation. During amino acid infusion nitrogen loss was not significantly greater than during intravenous feeding and less than that expected from isotonic dextrose infusion. However, we do not believe there is any indication at present for the introduction of isotonic amino acid infusions as a routine post-operative measure, but there may prove to be a place for these infusions in patients requiring prolonged intravenous therapy.

As a result of this survey and because of the risks and expense of parenteral nutrition we now manage our patients with isotonic glucose-saline after cystectomy. If, after 1 week, the patient is not immediately likely to return to oral feeding, total parenteral nutrition is commenced. Intravenous feeding is a valuable form of therapy but not without risk and should not be allowed to fall into disrepute from indiscriminate use.

Addendum

Five similar patients (mean age 65 years, mean weight 66 kg or 105% of ideal body weight) were studied subsequently on the third day after total cystectomy during an infusion of 3 litres of 4.3% glucose: 0.18% saline solution daily (129 g glucose/day). Estimated nitrogen loss was 0.17 g/kg/day (S.E.M.±0.02). This was significantly more than the negative balance in patients receiving parenteral nutrition ($p < 0.01$) but not significantly more than those receiving the isotonic amino acid solution.

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Polyglycolic Acid Versus Chromic Catgut in Bladder Surgery

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Summary—The clinical importance of calcified deposits on sutures in bladder surgery was evaluated in a blind paired randomised trial of 3/0 chromic catgut versus polyglycolic acid 3/0. Cystoscopy with photographic recording was performed 8 weeks after operation in 40 patients without and 8 patients with previous or present bladder stones. None had visible calcified deposits at that time and sutures were only visible in 1 patient from each of the 2 groups without bladder stones.

It was concluded that neither chromic catgut nor polyglycolic acid sutures carry any significant risk of bladder stone formation, whether infection is present or not; the conclusion includes both patients with and without previous bladder stones, but is less firm in the former because of the small number of patients studied.

For many years catgut has been the only absorbable suture material used in the urinary tract, but it is still not known whether the risk of calcification deposits on the sutures is of clinical importance. Recently, polyglycolic acid has replaced catgut and chromic catgut in many operations on the urinary tract because of reduced inflammatory reaction in the surrounding tissue (Morrow *et al.*, 1974) and higher knot security (Herrmann, 1973).

Animal experiments have shown that stones may be formed around catgut as well as polyglycolic acid sutures in the urinary tract of rats and rabbits, whether the urine is infected or not (Baur and Seuter, 1973; Bergman and Holmlund, 1973; Milroy, 1976). Calculi have not been seen around polyglycolic acid sutures in the bladder of the dog (Brannan *et al.*, 1973), but they have been noted around chromic catgut in these animals (Yudofsky and Scott, 1969).

The clinical importance of these observations is in dispute. Sebeseri *et al.* (1973) reported deposits on several catgut sutures 28 days after prostatectomy in 30 patients. The findings were documented by photographs. No stones were found on Dexon^R sutures, but the method of randomisation was not stated, nor was the frequency of deposits around the catgut sutures. Rusconi and Ciacci (1974) saw no calcification deposits on Dexon^R sutures during cystoscopy 30 days after bladder surgery in 52 patients.

To evaluate the clinical importance of calcium deposits on chromic catgut and Dexon^R sutures in bladder surgery the present controlled, randomised, blind trial was carried out, comparing the risks of calcium deposits on chromic catgut and Dexon^R sutures.

Patients and Methods

Forty-two patients who had an open bladder operation between August 1976 and May 1977 were admitted to the trial. Informed consent was obtained. Pre-operative investigations included measurement of urine pH and plasma creatinine, bacteriological examination of urine, intravenous pyelography and cystoscopy. Patients with no history of bladder stones and in whom no stones were found at operation were allocated at random to either atraumatic chromic catgut (Davis and Geck) 3/0 or atraumatic polyglycolic acid (Green Dexon^R) 3/0, using the blind paired sample principle. The same allocation was performed in patients with previous or present bladder stones as a group *per se*.

Two sutures with 3-throw knots were placed intravesically, immediately above the trigone, at an interval of 1 cm, including mucosal and muscular layer. Both sutures were cut 0.5 cm from the knot. The bladder was closed in 2 layers with

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interrupted 3-throw knots. The allocation was maintained for all bladder sutures except haemostatic sutures in the prostatic bed, which had a larger diameter but consisted of the material indicated by the random allocation.

Bacteriological examination of the urine was repeated at 1 and 7 weeks and cystoscopy with photographic recording was performed 8 weeks after the operation in all patients. The first author, who carried out the post-operative cystoscopies, was unaware of the suture material used. The presence of sutures, calcification deposits on these and pathology of the bladder mucosa seen during cystoscopy were recorded.

Five of the patients in whom a ureteric catheter was inserted during the operation also had cystoscopy 8 days post-operatively to remove the catheter.

The trial was planned to end if no deposits were seen in the first 40 patients having no previous or present bladder stones as demonstrated by the operation; otherwise a sequential analysis should be applied to end the trial.

Results

Forty-two patients without previous or present stones entered the trial. Two were later excluded, 1 because of death from pulmonary embolism 11 days after prostatectomy and the other because of unsuccessful photographic recordings. Pre-operative findings in the remaining 40 patients are recorded in Table 1. The patients were older in the catgut-group (median 72 years, range 50-84) than in the Dexon^R-group (56, 26-85).

Table 1 Pre-operative Findings in 40 Patients without Bladder Stones

	Dexon^R No. of patients	*Chromic Catgut No. of patients*
Men	14	18
Women	6	2
Urinary pH = 5	12	15
Urinary pH above 5	8	5
Bacteriuria		
significant ($\geq 10^5$/ml)	2	3
insignificant	1	0
none	17	17
Intravenous pyelography		
poor bladder emptying	5	11
bladder diverticula	1	3
Cystoscopy		
cystitis	4	4
hypertrophic prostate	6	13

Table 2 Type of Surgery and Findings at Follow-up

	Dexon^R No. of patients	*Chromic Catgut No. of patients*
Surgery		
Prostatectomy	5	14
Bladder resection	9	3
Transvesical ureterolithotomy	4	1
Others	2	2
Bacteriuria (7 weeks)		
significant ($\geq 10^5$/ml)	5	5
insignificant	0	1
none	13	11
not examined	2	3
Cystoscopy + photography (8 weeks)		
Sutures at site of cystotomy	0	1
Sutures just above the trigone	0	0
Calcification deposits	0	0
Irregular mucosa or hyperaemia at site of cystotomy	7	5
None of these	13	15
Cystitis	5	5
No cystitis	15	15
Healed prostatic bed	3	6
Prostatic bed not healed	2	8

Operations and findings at follow-up are presented in Table 2. One patient had a visible catgut suture at the site of cystotomy (Fig. 1), but was symptom free and without bacteriuria. Another patient had severe cystitis and the presence of a Dexon^R suture in the prostatic bed could not be excluded at 8 weeks; repeated cystoscopy at 12 weeks, after antibiotic treatment and dilatation of a meatal stricture, did not demonstrate any sutures.

Post-operative wound infection was seen in 1 patient in each of the 2 groups. Catgut sutures were macroscopically intact, while the Dexon^R sutures were beginning to break down (Fig. 2) in the patients examined 8 days after surgery. Seven weeks later no sign was found of catgut or Dexon^R sutures, except in the 2 cases mentioned above; irregular mucosa (Fig. 3) and hyperaemia (Fig. 4) were seen at the site of cystotomy in a small number of patients in both groups.

Eight patients with bladder stones were subjected to the same investigations (4 allocated to chromic catgut and 4 to Dexon^R) as the 40 patients. Neither calcification deposits nor sutures were visible during cystoscopy 8 weeks after surgery. Two patients in the Dexon^R group had significant bacteriuria at that time.

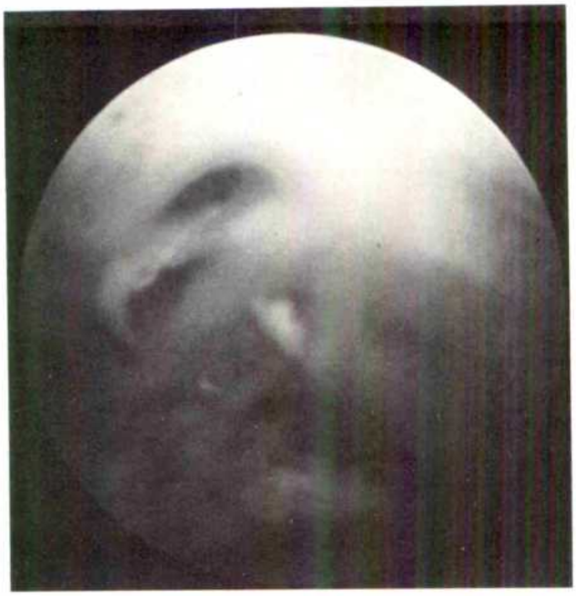

Fig. 1 Chromic catgut suture 8 weeks after cystotomy.

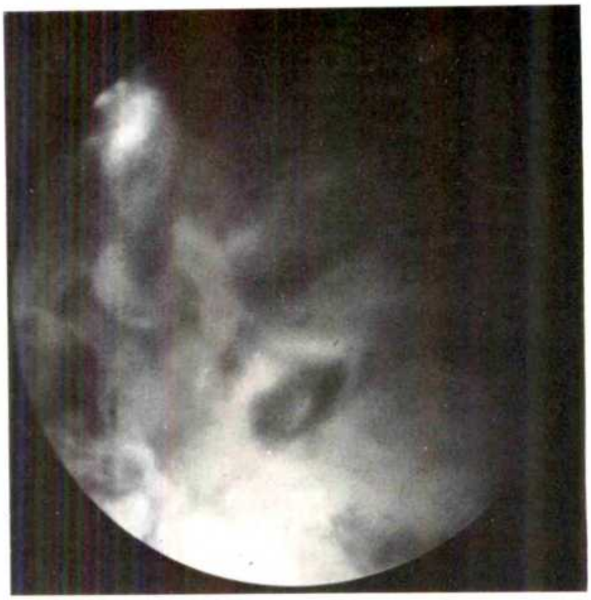

Fig. 2 Dexon^R suture 8 days after cystotomy.

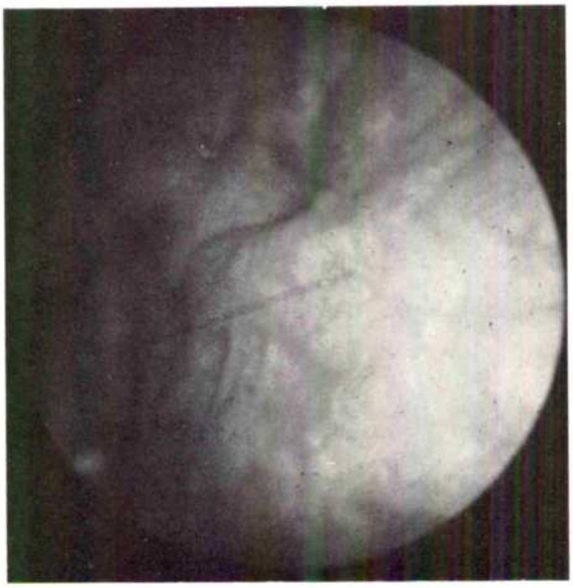

Fig. 3 Irregular mucosa at site of cystotomy 8 weeks after suture with Dexon^R.

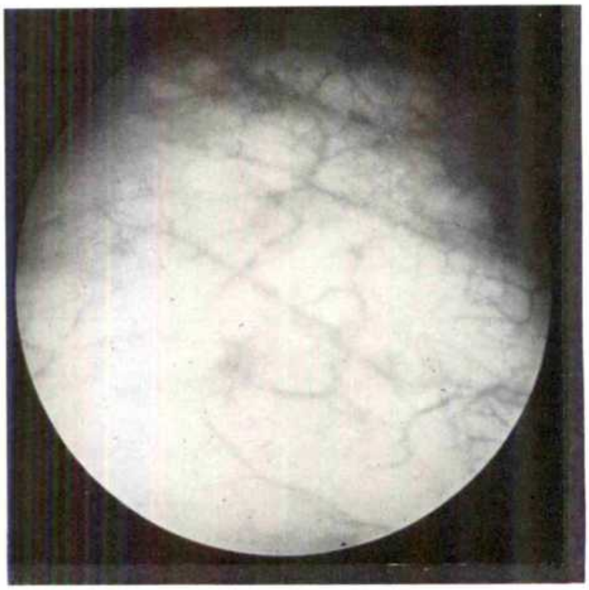

Fig. 4 Hyperaemic mucosa at site of cystotomy 8 weeks after suture with chromic catgut.

Discussion

No bladder stones were demonstrated in the present study, regardless of infection being present in 25% of patients in both groups. Both sutures caused some mucosal reaction but calcification deposits were not seen in these areas.

The results confirm other animal and human studies showing no sign of Dexon^R sutures 4 to 6 weeks after bladder surgery (Brannan *et al.*, 1973; Rusconi and Ciacci, 1974), and they also confirm that chromic catgut and polyglycolic acid sutures are difficult to find at gross examination at 8 weeks (Morrow *et al.*, 1974).

The high risk of calcification deposits on catgut sutures in dog experiments may have been due to the very long tails of sutures (Yudofsky and Scott, 1969). In clinical studies the presence of deposits may be explained by the earlier time of cystoscopy (Sebeseri *et al.*, 1973); deposits may have been expelled with the urine in our patients before the cystoscopy at 8 weeks, but if so they caused no clinical symptoms.

Similar results were obtained in the 2 groups in spite of the higher age and incidence of prostatic hypertrophy in the catgut group. The earlier breakdown of Dexon^R (Sebeseri *et al.*, 1975) was not followed by a greater number of postoperative complications than occurred with the use of chromic catgut. Wound infection was present in 1 patient from each of the groups and no fistulas were seen.

We conclude that the risks of permanent calcification deposits on chromic catgut and Dexon^R sutures in bladder surgery are similar and of minor clinical importance. This conclusion is valid both for patients with and without bladder stones, but is less firm in the case of the former.

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Adoptive Immunotherapy and Radiotherapy in the Treatment of Urinary Bladder Cancer

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Summary—Thirty-one patients with invasive transitional cell carcinoma of the urinary bladder were treated either by infusion of tumour immune pig mesenteric lymph node cells into the tumour blood supply, followed 6 weeks later by 5500 rad, or by radiotherapy alone. The patients were paired prior to treatment, using 4 criteria: age (nearest decade), sex, clinical stage (T3 or T4) and histological grade (average or high). The first patient in each pair then received combined treatment and the second radiotherapy alone. Administration of pig cells before radiotherapy offered no advantage to the patient in terms of the incidence of remission or the length of survival after treatment.

The theoretical rationale of attempts to transfer adoptive immunity, using lymph node cells, from a pig immunised against a human tumour, to the patient with that tumour have been discussed by Symes and Riddell (1973) and Prichard-Thomas and Symes (1978).

Previous reports from this department (Symes *et al.*, 1973; Feneley *et al.*, 1974) have described the use of tumour-immune pig lymph node cells in the treatment of patients with clinical Stage T3 or T4 transitional cell carcinoma of the bladder. Fourteen of 25 patients obtained clinical benefit as assessed by all of 3 criteria: a remission of symptoms, a reduction in tumour size and histological change in the tumour. The findings at that time were, however, of limited significance in that they described the outcome of treatment in individual patients without reference to appropriate controls.

Initially patients considered for immunotherapy, because of the advanced nature of their disease on initial presentation, received pig cells followed after an interval of 6 weeks by attenuated radiotherapy. The absence of serious side effects following this combined therapy led to radical radiotherapy being substituted for the attenuated dose. The interval of 6 weeks between immunotherapy and radiotherapy was chosen as a balance between allowing sufficient time to determine the initial anti-tumour effect of pig cells, and the need to commence radiotherapy without undue delay.

The aim of the present study was to determine whether infusion of tumour-immune pig cells into the tumour blood supply, prior to the giving of radical radiotherapy, offered any advantage over the administration of radiotherapy alone.

Patients and Methods

Patients on their initial presentation were matched according to 4 criteria: sex, age (within a decade), clinical Stage T3 or T4 and histological grade, average or high. Histological grading was carried out according to the criteria of Miller *et al.* (1969)

Treatment groups

Thirty-one matched patients were allocated to 1 of 2 treatment groups:

(1) Infusion of pig cells, followed after an interval of 6 weeks by 5500 rad—16 patients.
(2) Radical radiotherapy, 5500 rad in 25 daily fractions over a period of 5 weeks—15 patients.

Allocation for groups (1) and (2) was such that the patients were paired. The first patient in the pair then received combined treatment and the second radiotherapy alone.

Radiotherapy was given, following localisation

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of the bladder by air contrast cystography, using an 8 MeV linear accelerator or telecobalt apparatus.

The details of the preparation and administration of pig lymph node cell suspensions have previously been described (Symes and Riddell, 1973).

Patient assessment

Initial. Immediately prior to the commencement of treatment each patient was assessed as follows:

1. For symptoms, with particular reference to haematuria, pain with micturition, frequency and incontinence.
2. By excretion urography. The presence of a space-occupying lesion in the bladder, deformity of the bladder wall or obstruction of the intramural ureter on the side of the growth were noted.
3. At cystoscopy and bimanual examination, under anaesthesia, the size, consistency and fixation or tethering of the tumour were assessed.
4. A substantial biopsy of the tumour was obtained by transurethral resection.

After treatment. For patients receiving pig cells prior to radiotherapy, the first assessment after treatment was carried out at 6 weeks, *i.e.* immediately prior to the commencement of radiotherapy.

All patients were further assessed 3 months after radiotherapy, and thereafter at intervals of 6 months.

Each assessment after treatment comprised the same 4 modalities described in the initial assessment.

Evaluation of progress

The period of any remission in the course of the disease was noted for each patient. To qualify for acceptance, a remission had to satisfy *all* of the following criteria:

(1) Partial or complete remission of symptoms.
(2) Objective evidence of a reduction in tumour size. In order to eliminate any equivocal assessment, complete remission was defined as disappearance of the tumour on endoscopic and bimanual examination under anaesthesia. This was supported, where appropriate, by relief of ureteric obstruction and/or a reduction in the size of the intravesical filling defect seen on excretion urography. Where the reduction in tumour size was less than 50% the remission was designated as partial.
(3) Evidence of histological change in the tumour by comparison with the pre-treatment biopsy. This change consisted of substantially increased necrosis, together in some cases (Feneley *et al.*, 1974) with an infiltration around the tumour of multinucleated giant cells and/or eosinophils. However, where cystoscopy and bimanual examination revealed no evidence of persistence of a tumour and an apparently healthy bladder, a mucosal biopsy was not performed.

The survival time of each patient following treatment was noted.

Results

Of the patients in group (1) (tumour-immune pig lymph node cells +5500 rad) 10/16 showed a remission (Table 1). This compared with 9/15 remissions among the patients in group (2).

The absence of a significant difference in remission rates is supported by the equivalent survival times, following treatment, of patients in the 2 treatment groups. As the patients in the 2 groups were compared (with one exception) as a series of matched pairs, they were evenly

Table 1 Details of remissions among 16 patients with Stage T3 or T4, average or high grade, transitional cell carcinoma of the urinary bladder, treated by intra-arterial infusion of tumour-immune pig lymph node cells, followed after an interval of 6 weeks by 5500 rad

Remission of Symptoms		*Partial*		*Complete*
Frequency		0		1/5*
Pain with micturition		0		0/4
Haematuria		0		8/12
	Partial remission			
Evidence of a reduction in tumour size	Nil	<50%	>50%	Complete
Endoscopic assessment	4/13*	4/13		5/13
Bimanual examination under anaesthesia	8/13		1/13	4/13
Histological changes		−ve	+ve	
Necrosis		7/11*	4/11	
Infiltration of giant cells		7/11	4/11	
Infiltration of eosinophils		9/11	2/11	

* Denominator is the number of patients whom it was possible to assess using this criterion, *i.e.* the number of patients initially presenting with this symptom or sign, or from whom appropriate biopsy specimens were available.

Table 2 Details of remissions among 6 patients with Stage T3 or T4 average or high grade transitional cell carcinoma of the urinary bladder, treated by intra-arterial infusion of tumour-immune pig lymph node cells, followed after an interval of 6 weeks by 4000 rad

Remission of Symptoms		*Partial*	*Complete*	
Frequency				
Pain with micturition		0	3/3*	
Haematuria		0	3/3	
	Partial remission			
Evidence of a reduction in tumour size	Nil	<50%	>50%	Complete
Endoscopic assessment			1/6*	5/6
Bimanual examination under anaesthesia			1/6	5/6
Histological changes		−ve	+ve	
Necrosis		1/2*	1/2	
Infiltration of giant cells		1/2	1/2	
Infiltration of eosinophils			2/2	

* Denominator is the number of patients whom it was possible to assess using this criterion, *i.e.* the number of patients initially presenting with this symptom or sign, or from whom appropriate biopsy specimens were available.

stratified. Thus the number of patients surviving, at succeeding times after the commencement of treatment, is compared by the 2 lines, one for each treatment group, in Figure 1. In addition individual pairs of patients were compared as to their remission and survival times in Figure 2. Although it is obvious that the giving of tumour-immune pig lymph cells prior to radiotherapy offered no advantage over treatment by radical radiotherapy alone, the combined treatment was not disadvantageous either.

Discussion

It was found that pig mesenteric lymph node cells, immunised against the tumour to be treated, and injected into the arterial blood supply of the tumour, when followed 6 weeks later by a radical course of radiotherapy, did not confer significant clinical benefit on the patient as compared with the effect of radical radiotherapy alone. This was assessed in terms of the remission rate and survival time. It is of interest, however, that in the patients receiving combined treatment 6 of the observed remissions were established at 6 weeks, that is before the commencement of radiotherapy.

Evidence that the pig cells must be immunised has been provided by experiments involving the treatment of mouse tumours (Prichard-Thomas and Symes, 1978). In those experiments pulmonary metastases were induced in A strain mice by iv injection of A strain mammary carcinoma cells. Three days later the mice received local thoracic irradiation, and 7 days later pig cells iv. The pig cells were either non-immune or tumour immune and only the latter reduced the number of metastases assessed on day 14. It was also shown that the pig cells had to be immunised against mouse tumour or skin; immunisation against a human tumour was ineffective in inducing anti-tumour activity.

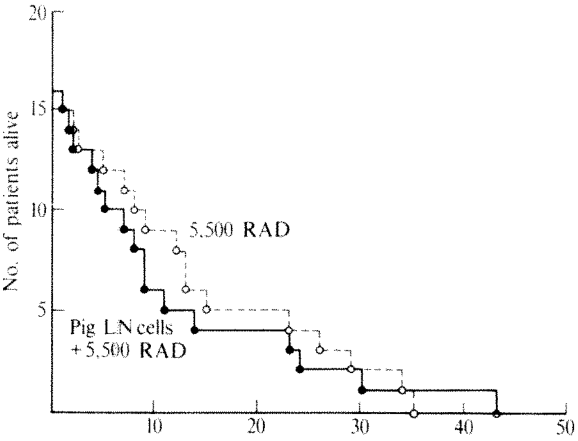

Fig. 1 The number of patients with transitional cell carcinoma of the bladder living at succeeding times after treatment. Sixteen patients were treated with tumour-immune pig lymph node cells followed at 6 weeks by radiotherapy and 15 patients received radiotherapy alone. The patients in the 2 treatment groups were paired (with one exception) according to age, sex, stage (T3 or T4) and histological grade (average or high).

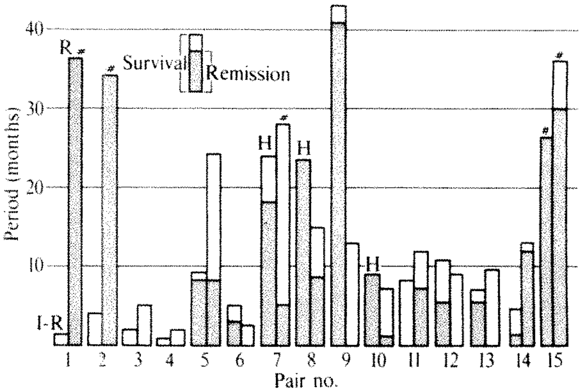

Fig. 2 Details of the comparative remission and survival times in the 15 pairs of patients depicted in Figure 1. The first patient in each pair received combined treatment, the second radiotherapy alone. # Patient still alive. H. Giant cells present in biopsy 6 weeks after treatment.

It is therefore suggested that the initial anti-tumour effect is dependent on the adoptive transfer of immunity from the pig to the patient. However, Feneley *et al.* (1974) suggested that the attendant reaction between immunised pig cells and tumour target cells might result in the liberation of lymphokines capable of activating host macrophages. These activated macrophages would then produce further tumour destruction. Multinucleated giant cells have been seen in tumour biopsies from a number of patients 6 weeks after injection of pig cells, *i.e.* immediately before the commencement of radiotherapy. The presence of such cells was associated with an eventual favourable response to treatment.

If there is a second stage of tumour destruction, due to activated host macrophages, it would seem reasonable that attenuated radiotherapy would interfere less with this than radical radiotherapy. This hypothesis is supported by preliminary results in which 6 patients with Stage T3 or T4 tumours were treated with pig cells followed after 6 weeks by attenuated radiotherapy (4000 rad). All 6 patients showed a remission and in 5 this was complete (Table 2) and persisted for at least 1 year. The result of the present controlled trial comparing combined treatment with pig cells and radical radiotherapy, with radical radiotherapy alone, was unequivocally negative. However, preliminary data using pig cells combined with attenuated radiotherapy make us feel justified in performing a new prospective trial.

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Alpha-Adrenergic Agents in Urinary Disorders of the Proximal Urethra

Part I. Sphincteric Incontinence

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Summary—Phenylpropanolamine, an alpha receptor stimulant, was found effective in 11 of 13 female and 6 of 7 male patients with sphincteric incontinence. In all the male patients except 1, the incontinence has followed prostatectomy.

Side effects occurred in only 1 patient.

As a rule, the beneficial response depended on the therapy being continued.

The results are consistent with the distribution of alpha receptors and their effect in the proximal urethra.

Laboratory studies have demonstrated a predominance of alpha-adrenergic receptors in the bladder neck and proximal urethra in man (Nergardh and Boreus, 1972; Awad *et al.*, 1974; Caine *et al.*, 1975). It has also been shown, using the urethral pressure profile method, that blocking these receptors reduces the profile pressure (*i.e.* wall tension) along the whole length of the proximal urethra, particularly in the peak pressure zone (Donker *et al.*, 1972; Awad *et al.*, 1976). This zone corresponds to the mid-urethra in the female and the region of the verumontanum in the male, where it is also referred to as the "distal sphincter mechanism" (Turner-Warwick, 1975). Female patients with sphincteric incontinence show a reduction in urethral closure pressure (Enhorning, 1961; Gleason *et al.*, 1974; Awad *et al.*, 1977). In the male, sphincteric incontinence is rare; the commonest cause is prostatectomy. Incompetence of the "distal mechanism" is recognised as the reason for stress urinary incontinence when it occurs after prostatectomy. In view of the available data on the distribution of alpha receptors in the proximal urethra and their effect, it is rational to use alpha agonists in the presence of sphincteric incontinence to reinforce the sphincteric mechanism in female and post-prostatectomy male patients.

Ephedrine (Rashbaum and Mandelbaum, 1948; Diokno and Taub, 1975) and Ornade^{R} (Smith, Kline and French Ltd), a compound that contains phenylpropanolamine—an alpha agonist (Stewart *et al.*, 1976), have been tried in patients with sphincteric incontinence with a reasonable degree of success. We herein report our experience on the use of phenylpropanolamine, in its pure form, in this condition.

Material and Method

Seven males and 13 females with sphincteric (stress) incontinence were treated. In 6 of the male patients the incontinence followed prostatectomy and in the remaining patient was secondary to myelodysplasia (Table 1). The cystogram of this patient showed an incompetent bladder neck (Fig. 1), not unlike post-prostatectomy patients. The post-prostatectomy patients had all been operated upon more than 1 year previously. The 13 female patients who entered the study were selected for a variety of reasons (Table 1).

The pre-treatment evaluation of the female patients included a cystometrogram, a stress

Table 1 Material

Males (7)			*Females (13)*	
Post-prostatectomy		6	Poor surgical risk	4
radical	2		Refused surgery	3
simple	4		Failed surgery	3
Myelodysplasia		1	Modest degree	3

Read at the 33rd Annual Meeting of the British Association of Urological Surgeons in Aberdeen, June 1977.

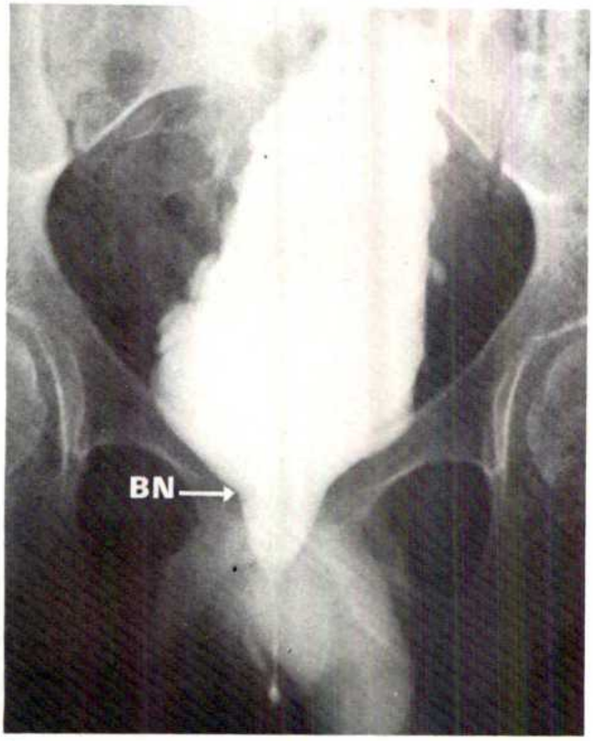

Fig. 1

cystogram and a urethral pressure profile in addition to the clinical assessment. All male patients had a cystometrogram and 4 had a urethral pressure profile. None of the patients had a significant amount of residual urine (less than 10 ml) or urinary tract infection. Hypertension and a history of thyroid dysfunction were also excluded.

Therapy consisted of phenylpropanolamine 50 mg tid. Approximately 4 weeks after starting therapy the clinical response, blood pressure and any side effects were recorded. If the patient complained of hesitancy or difficulty in urinating, the volume of residual urine was determined. In some patients urethral pressure profile examination was performed.

Table 2 Results

	Females (13)	*Males (7)*
Good	8	2
Improved	3	4
Failed	2	1

Table 3 Urethral Pressure Profile (6 Females)

		Pre-treatment	*Post-treatment*	*Percentage increase*
Maximum closure Pressure (cm H_2O mean ± SEM)	E	47 ± 8	72 ± 15*	79 ± 25
	F	43 ± 10	58 ± 13 †	65 ± 43
Mean pressure Continence zone (cm H_2O mean ± SEM)	E	5.6 ± 0.8	9.8 ± 2.0*	76 ± 22
	F	6.4 ± 1.6	8.3 ± 1.5 †	61 ± 29

* Significant difference between means ($P < 0.05$).
† No significant difference between means ($0.05 < P < 0.1$).
E = Empty bladder F = Full bladder

Results

The response to therapy is shown in Table 2. A "good" result meant the patient became totally dry. Those who "improved" were incontinent only with severe physical activity. When a beneficial response occurred, it was noticed by the patient immediately on starting therapy or within a few days. It was apparent when the patients were interviewed that if several doses were omitted the incontinence tended to recur. Only 1 female patient has been able to discontinue her medication after 3 months of therapy and she has remained continent. The incidence of side effects was low; only 1 of the 20 patients developed headaches and dizziness which necessitated stopping her treatment. None of the patients developed hypertension. The volumes of residual urine when measured were always insignificant.

In 6 female patients who responded, a urethral pressure profile was carried out while on therapy and the changes in maximum closure pressure (Hald *et al.*, 1976) and the mean pressure in the continence zone (Gleason *et al.*, 1974) with empty and full bladders are shown in Table 3. Only 2 male patients consented to a profile examination while on therapy and their closure pressures showed similar increases.

Discussion

Phenylpropanolamine is present in several common cold remedies in combination with other drugs. Stewart *et al.* (1976) used Ornade^R, a compound that also contains chlorpheniramine maleate (an antihistamine) and isopropamide iodide (an antimuscarinic agent). These drugs could produce unnecessary side effects. Thus, for sphincteric incontinence phenylpropanolamine should be administered in its pure form.

Although the starting dose was always 50 mg 3 times a day, several patients were able to omit the evening dose without any noticeable regression in their symptoms. Patients were often able to gauge the time to take the drug, depending on their physical activity. In 1 male patient the dose had to be increased to 75 mg tid after the first month. A significant limitation with this method of treatment appears to be the need for the patient to stay on the medication. However, long-term therapy seems to be well tolerated and the drug does not lose its effect. It is interesting to note that of the 7 male patients there was only 1 failure. Considering the degree of incompetence of the bladder neck in these patients, the effect of the drug was probably on the distal mechanism. This is consistent with the observation made previously, that the sympathetically innervated smooth muscles are probably a significant component in this region (Donker *et al.*, 1972; Awad *et al.*, 1976).

It is important to document the patient's response objectively, *e.g.* by the urethral pressure profile. Although the number of patients we examined was small the increase in profile pressures was constant. However, the difference in means did not reach statistical significance in the profiles done with full bladders (Table 3). The percentage increase in mean closure pressure was comparable to that in maximum closure pressure. This is consistent with the distribution of alpha receptors in the proximal urethra (Donker *et al.*, 1972; Awad *et al.*, 1976).

A similar beneficial response to alpha agonists was reported in previous series. Rashbaum and Mandelbaum (1948), using ephedrine in female patients with stress incontinence, reported that 40% of the patients were cured and 41% improved. They recommended that ephedrine could be used as a therapeutic test to differentiate "false" from "true" stress incontinence. The incidence of side effects was not mentioned. Diokno and Taub (1975) also used ephedrine in both male and female patients with urinary incontinence, including those with neurological lesions. Eleven of 38 patients were considered failures, 3 because of side effects. Stewart *et al.* (1976), using Ornade^R, reported a success rate of 59% in female and 27% in male patients. They felt the results with post-prostatectomy patients were discouraging. Of 88 patients 9 developed side effects. Although the number of patients in the present series is smaller, the results appear to be superior. A possible reason for this is that phenylpropanolamine given alone has fewer side effects and is better tolerated than Ephedrine or Ornade^R, even if larger doses are needed. Since the drug does not have a long-lasting effect, continuous therapy is necessary to maintain the response. This was not emphasised in previous series. In our opinion this is a significant limitation and should be taken into consideration in the long-term management of the patient.

From this limited experience we feel that phenylpropanolamine should be used in all male patients with sphincteric incontinence, provided there are no contraindications. It is recognised that surgical treatment of sphincteric incontinence in the male is not a simple task and has a relatively high failure rate. A good response to medication would make surgery unnecessary. In female patients surgical treatment, because of its high success rate, should be the treatment of choice. However, drug therapy should be considered when (1) the degree of sphincteric incompetence is mild as assessed clinically or by the urethral pressure profile, (2) the patient is a poor surgical risk or refuses surgery and occasionally (3) as a therapeutic test when the diagnosis, despite thorough investigations, remains inconclusive and (4) in patients where surgery has failed. However, in cases where extensive surgical damage to the urethral smooth muscle has taken place there may not be a significant response.

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Alpha-Adrenergic Agents in Urinary Disorders of the Proximal Urethra
Part II. Urethral Obstruction due to "Sympathetic Dyssynergia"

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Summary—Lower urinary tract obstruction in patients with neurological lesions can be due to "sympathetic dyssynergia".

The obstruction can be at the level of the external sphincter.

Phentolamine (i.v.) used during the voiding cystourethrogram helps to make the diagnosis.

Phenoxybenzamine therapy produced improvement in 10 of 18 patients.

As a rule, patients had to continue on the drug to maintain their response.

The evidence for the presence of sympathetically innervated smooth muscle in the bladder neck and proximal urethra and the contribution of this innervation to urethral closure in man was reviewed in Part I (Awad *et al.*, 1978). Previous workers have demonstrated that phenoxybenzamine (POB), an alpha receptor blocking agent, can be effective in relieving lower urinary tract obstruction in patients with neurological disorders (Krane and Olsson, 1973; Stockamp and Schreiter, 1975; Mobley, 1976). Phentolamine, which is also an alpha-receptor blocking agent, can be used as a test, in combination with uroflowmetry (Olsson *et al.*, 1977), or voiding cystourethrography (VCU) (Awad and Downie, 1977), to detect lower tract obstruction due to sympathetic dysfunction and thus to help select patients who would probably benefit from phenoxybenzamine therapy. The term "sympathetic dyssynergia" was suggested to describe this dysfunction by analogy to the somatic system (Awad and Downie, 1977). Abel *et al.* (1974) demonstrated that urethral obstruction in cauda equina lesions can be sympathetically mediated.

Traditionally, sympathetically innervated smooth muscle has been considered to be limited to the bladder neck. As discussed previously (Awad and Downie, 1977; Awad *et al.*, 1978), this concept is erroneous and the so-called region of the external urinary sphincter is significantly affected by alpha-adrenergic agents (Donker *et al.*, 1972; Awad *et al.*, 1976).

The present study was carried out to evaluate the role of POB in the treatment of patients with lower urinary tract obstruction associated with neurological lesions. A specific objective was to determine if the drug can be effective when the obstruction appears to be in the region of the external sphincter.

Material and Method

Eighteen patients with neurogenic bladder dysfunction and obstruction who have received POB therapy form the basis of this report. Twelve of these patients had upper (UMN) and 6 lower (LMN) motor neurone lesions. The causes of the neurological lesions are listed in Table 1. All patients with UMN lesions and 3 of the patients with LMN lesions were males. All patients had large volumes (300-500 ml) of residual urine.

Table 1 Causes of the Neurological Lesions

Upper motor neurone (12):	Trauma	10
	Transverse myelitis	2
Lower motor neurone (6):	Trauma	1
	Surgical	3
	Myelodysplasia	2

Read at the 33rd Annual Meeting of the British Association of Urological Surgeons in Aberdeen, June 1977.

Table 2

Level of obstruction on the VCU		*Results of phentolamine test*		
		Positive	*Inconclusive*	*Side effect*
Bladder neck:	5*	2	2	–
External sphincter:	9	7	1	1

* The phentolamine test was not done in 1 patient.

Three patients had associated upper tract changes, hydroureters and various degrees of hydronephrotic changes. Two other patients had autonomic dysreflexia. In 1, the dysreflexia occurred only when he was sitting.

Cystometrograms in the patients with UMN lesions demonstrated uninhibited detrusor contractions and in those with LMN lesions decreased detrusor compliance and reduced capacity. Detrusor hypotonicity was thus excluded in all patients. Fourteen of the 18 patients had a VCU; in 9 (8 UMN and 1 LMN), the obstruction appeared to be in the region of the external sphincter and in 5 (3 UMN and 2 LMN) the obstruction appeared to be at the bladder neck (Table 2). The effect of phentolamine on the VCU was examined in 13 of the 14 patients. Cystourethroscopy confirmed the presence of trabeculation in all patients and ruled out the presence of a stricture or significant prostatic hypertrophy in the adult males.

The dose of POB was 10 mg twice daily for 2 days and, if this was tolerated and hypotension did not develop, it was increased to 3 times daily. Only rarely was the dose increased to 4 times daily. The 2 children with myelodysplasia were started on a smaller dose (2.5 mg daily); this was increased to 5 mg in 1 child.

Most patients were hospitalised at the start of therapy and residual urine and side effects were closely monitored. In those who had upper tract changes intravenous pyelograms were done 1 month after beginning therapy and every 3 to 6 months thereafter. The rest had pyelograms every 6 to 12 months.

Results

A patient was judged to have a positive response to phentolamine if he was able to void before and after the drug and the obstruction evident on the initial VCU was at least partially relieved after phentolamine (Awad and Downie, 1977). If there was no change in the obstruction, it indicated a negative response. On the other hand, if the patient failed to void, either before or after the drug, the test was considered inconclusive. The results of the test are shown in Table 2. In 7 of the 9 patients who had a positive response, the obstruction was in the so-called region of the external sphincter. One patient developed significant hypotension and the examination had to be discontinued and in 3 patients the test was inconclusive. Patients with a negative response to phentolamine did not receive POB therapy and therefore are not included in this report.

The response to treatment is shown in Table 3. A "good" response meant a reduction in residual urine to less than 100 ml and a "fair" response to less than 200 ml. The 3 patients with upper tract changes showed improvement. The symptoms of autonomic dysreflexia were relieved in 1 patient but there was no improvement in the patient in whom the dysreflexia was related to posture. Of the 10 patients who had a good or fair response to POB, 8 had VCU prior to therapy and in 7 of these the obstruction was in the region of the external sphincter.

Table 4 shows the correlation between the response to phentolamine in the 13 patients who had the examination, and the response to POB therapy. It appears that those who had a positive response to phentolamine improved on POB and the only failures were due to side effects. The 3 who had an inconclusive response did not fare as well.

Table 3 Results of Phenoxybenzamine Therapy

	UMN—12	*LMN—6*
Good	6	2
Fair	2	0
Poor	4 (1)*	4 (4)*

* Number of poor results because of side effects.

Table 4

Phentolamine test		*Response to Phenoxybenzamine*		
		Good	*Fair*	*Poor*
Positive	9	5	1	(3)*
Inconclusive	3		1	2
Side effect	1			(1)*

* Number of poor results because of side effects.

Table 5

Side effects 5/18	
Hypotension	2
Severe nasal congestion	1
Sphincteric incontinence	2

The side effects and their incidences are listed in Table 5. Two of 3 female patients with LMN lesions developed sphincteric incontinence while on therapy, although they were continent beforehand. Their incontinence ceased when the drug was discontinued.

A significant observation was that 9 of the 10 patients in this series who responded to POB had to continue on the medication to maintain their response. A reduced dosage of 10 mg twice daily was sometimes possible in these patients.

Discussion

This study confirms the previous observation that in certain patients with neurological disorders and lower urinary tract obstruction the obstruction can be relieved by alpha-adrenergic blocking agents (Krane and Olsson, 1973; Stockamp and Schreiter, 1975; Mobley, 1976). It is concluded that the obstruction in these patients is due to unco-ordinated sympathetic activity during voiding, referred to here as "sympathetic dyssynergia". The fact that, in many of the patients who responded, the obstruction was in the region of the external sphincter supports the previous findings of a significant sympathetic component in this region (Donker *et al.*, 1972; Awad *et al.*, 1976; Awad and Downie, 1977). Pharmacological and morphological studies have also demonstrated these findings in experimental animals (Awad and Downie, 1976; Dixon and Gosling, 1977).

We feel that examining the effect of phentolamine on the VCU in the presence of obstruction is a worthwhile diagnostic step. There was a good correlation between the immediate, short-lasting response to phentolamine and the response to POB therapy. Since both these agents are alpha-blockers, such a correlation is not surprising. The success of the test depends on the ability of the patient to void before and after phentolamine is given. If a patient is able to initiate micturition *only* after phentolamine, one should be cautious in calling this a positive test. The initiation of micturition depends on other factors, most important of which is the triggering of a detrusor contraction. Thus, if a patient is unable to void, either before or after the phentolamine, the test is considered inconclusive. We have not felt justified in treating patients with POB if they had a negative response to phentolamine and thus we cannot comment on the incidence of false negatives with this test.

Important limitations of POB therapy were observed in this series. In contrast to other series (Krane and Olsson, 1973; Mobley, 1976), a beneficial response occurred in only approximately half of the patients. We also found that the incidence of side effects is significant and was relatively high in patients with LMN lesions. In addition, many of the patients who improved had to remain on the drug to maintain their response. We feel the drug is very valuable in potentially reversible conditions. If continuous therapy is necessary, other methods of treatment such as intermittent catheterisation or surgery (transurethral sphincterotomy or bladder neck resection) should be considered. POB may prove to be a useful adjunct to intermittent catheterisation or when surgery has failed. Additional experience is, however, necessary before the role of POB therapy is clearly defined.

The disorder herein referred to as "sympathetic dyssynergia" has not been thoroughly investigated. Important aspects such as pathophysiology, incidence, and natural history need clarification. Such data will probably improve patient selection and therapeutic planning. The finding that obstruction at the level of the external sphincter can be due to this disorder significantly expands its clinical relevance.

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Congenital Parameatal Urethral Cyst in the Male

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Summary—Three cases of parameatal cysts in boys are reported. Two cysts were present at birth and the other was found in early infancy. Aetiology and treatment are discussed.

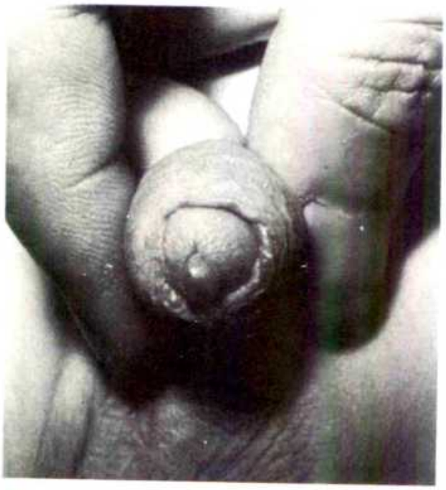

Fig. 1a

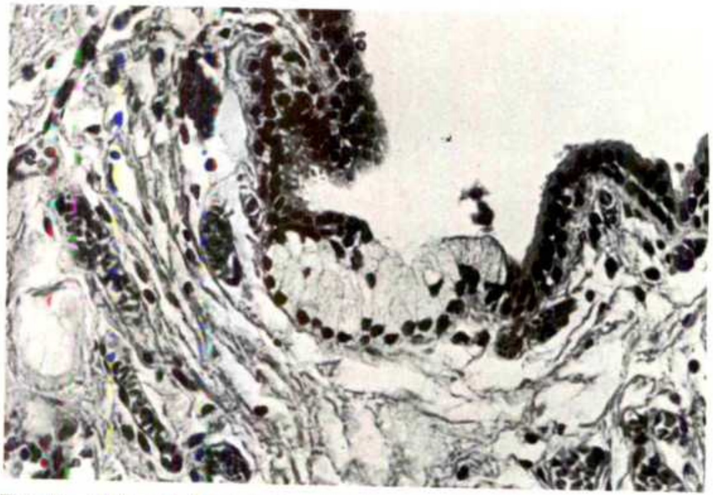

Fig. 1b. H.E. staining (×200).

Cyst formation in the parameatal area of the male urethra is uncommon. Three cases have been observed in boys in the past 7 years.

Case reports

Case 1. K.Y., aged 14 years, presented on 9 March 1972 with an 8×9 mm cyst on the left side of the urethral meatus. His mother became aware of the cyst in his early infancy because of irregularity and spraying of his urinary stream. There was no dysuria nor urinary frequency. About 4 years prior to admission, simple aspiration of the cyst had been carried out at another hospital but the lesion recurred within a few weeks. The cyst was excised using the electrocautery with needle point under spinal anaesthesia. Post-operative progress was uneventful. Histological examination showed a lining of transitional epithelium with no evidence of infection.

The cyst did not recur during a 7 year follow-up.

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Case 2. S.Y., aged 5 years, was hospitalised on 30 June 1976, complaining of spraying of urine during micturition and a 3×4 mm cyst on the left side of the urethral meatus. The cyst had been present at birth and gradually became more prominent. It was excised completely under general anaesthesia.

Histological examination showed a tall columnar epithelial lining with no evidence of infection. Post-operative progress was uneventful. At follow-up 18 months later there was no recurrence.

Case 3. K.I., aged 3 years, presented on 10 November 1977 with a 5×5 mm cyst on the left side of the urethral meatus (Fig. 1a). His mother said that the cyst had been present at birth. During urination the urine was often sprayed and pain occurred when the cyst rubbed on the underclothes.

The cyst was excised completely under general anaesthesia. Histological examination revealed a lining of tall columnar epithelium with no evidence of infection. The epithelium and the cyst content showed positive staining with periodic acid Schiff (PAS), suggesting the existence of mucus-secreting glands (Fig. 1b). Post-operative recovery was uneventful. Follow-up 6 weeks post-operatively revealed no recurrence.

Discussion

Shiraki (1975) considered that parameatal cysts in the male arise from the occlusion of paraurethral ducts and that the development of the cyst is unrelated to trauma, infection or circumcision. Hill and Ashken (1977) suggested that infection could be an aetiological factor. The former opinion seems more acceptable in our cases because there was no evidence of infection, 2 cysts had been present at birth and another was found in early infancy.

Simple aspiration of the cyst resulted in recurrence in our Case 1. Good results were obtained with complete excision.

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Recanalisation of Vas after Vasectomy. Evaluation of Various Techniques in Dogs

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Summary—A critical study of various techniques for end-to-end vaso-vasostomies without or with internal splints on 41 dogs is presented. The results of vaso-vasostomy without any internal splint were significantly better than those with splints, both for primary as well as secondary repair after 6 weeks.

The presence of an internal splint was associated with a high incidence of severe infection in the vas, epididymis and testis. An end-to-end mucosa-to-mucosa anastomosis using either 6/0 silk or Prolene under magnification is recommended as a simple and successful method of recanalisation of the vas in clinical practice.

The surgical literature from 1930 to 1950 reveals only a few reports of isolated cases or short series of vaso-vasostomies on humans (O'Conor, 1948). With the widespread use of vasectomy for sterilisation, there has been a resurgence of interest in re-anastomosis of the vas deferens (O'Conor, 1961; Roland, 1961; Waller and Turner, 1962; Derrick *et al.*, 1973; Dorsey, 1973). Following the pioneering studies of Phadke and Phadke (1967), end-to-end vaso-vasostomy with an internal splint has been advocated in the majority of the clinical reports on this subject. Many theoretical advantages are attributed to the presence of the internal splints. However, the techniques advocated are contrary to the accepted principles of repair for small vessels, ureter and common bile duct.

In this experimental study an attempt has been made to evaluate the various techniques used for vaso-vasostomy and evolve a simple and successful method suitable for clinical use.

Material and Methods

The study was undertaken on 41 adult healthy male mongrel dogs, weighing 12 to 15 kg. The animals were anaesthetised by either intravenous Pentothal 20 mg/kg or Nembutal 25 mg/kg. The cord was exposed through a paramedian incision parallel to the penis and about 3 to 4 cm of vas deferens isolated from its blood supply above the testis. A 1 cm segment of the vas was excised. A testicular biopsy was also performed.

The vaso-vasostomy was performed using 5 to 6 interrupted sutures through the sero-muscular coat with the aid of magnifying spectacles (Occulus) (Fig. 1).

The experiments were in 2 groups.

In group I, end-to-end vaso-vasostomy was performed on 21 dogs in 4 subgroups using 4 techniques (Table 1). Two types of suture material (6/0 silk (Ethicon, W 815) on reverse cutting curved needles 10 mm, or monofilament nylon 8/0 on 8 mm curved cutting needles) were used in techniques I and II. In techniques III and IV, internal splints either 2/0 monofilament nylon suture on 1 side or polythene tubing No. 00 (Portex) were used with 6/0 silk and 8/0 monofilament nylon sutures respectively. The splints were introduced by attaching them to a fine straight needle or fixing to the tubing. Each was placed into the lumen by piercing the wall 1.5 cm proximally and then into the lumen of the distal vas and out through its wall about 1 to 2 cm distally (Fig. 2). These splints were removed under anaesthesia after 10 days.

In group II, at the first stage, the 2 ends of the vas were ligated with black silk to facilitate identification and a testicular biopsy was performed. The cord was re-explored after 6 weeks and the 2 ends of the vas were identified, dissected and held on moist tapes. The fibrosed ends were excised transversely to expose the healthy vas on

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Table 1 Technique of Vaso-Vasostomy

Group I: Immediate repair			*Group II: Secondary repairs*		
Technique	*Procedure*	*No. of vasa*	*Technique*	*Procedure*	*No. of vasa*
I	Silk 6/0	10	V	Silk 6/0	10
II	Monofilament nylon 8/0	10	VI	Prolene 6/0	10
III	Silk 6/0 + splint		VII	Silk 6/0 + splint	
	(a) Polythene tube No. 00	6		(a) Polythene tube No. 00	5
	(b) Monofilament nylon 2/0	5		(b) Monofilament nylon 2/0	5
IV	Nylon 8/0 + splint		VIII	Prolene 6/0+splint	
	(a) Polythene tube No. 00	6		(a) Polythene tube No. 00	5
	(b) Monofilament nylon 2/0	5		(b) Monofilament nylon 2/0	5
	Total=	42		Total=	40

either side. The patency of the distal vas was confirmed by injection of saline through a syringe. The 20 dogs studied in this group were divided into 4 subgroups of 5 dogs each. Secondary vaso-vasostomy was carried out as outlined in group I, except that 6/0 Prolene sutures on 13 mm curved eyeless needles (Ethicon, 8706) were used in place of 8/0 monofilament nylon.

In techniques I and II, the spermatic tract including the testis from 1 side was removed *en bloc* after 4 weeks and the other side after 6 to 8 weeks. In the remaining experiments, both sides were removed simultaneously after 6 weeks by ligation of the cords as high up as possible.

After removal, the cut end of the vas distal to the anastomosis was isolated. A No. 26 blunt hypodermic needle was introduced into the lumen. A retrograde vaso-epididymography was performed using 1 ml of "Visotrast 290".

The tissues were preserved in buffered 10% formation. Histopathological examination of the vas at the site of anastomosis, epididymis and testis was carried out by standard techniques. A statistical evaluation of the results using a chi-square test was carried out.

Results

In group I, 42 studies in 21 dogs were available for analysis. In 2 dogs (Nos. 7 and 23) different operations were performed using a polythene tube on each side, which accounted for 6 experiments using techniques III(a) and IV(a). The radiographic and pathological study of the vas removed after 4 weeks showed a higher incidence of leakage and inflammatory change, with local thickening and adhesions, suggestive of incomplete healing. The plan of study was therefore modified and all subsequent specimens were removed after 6 weeks. There was complete disruption of the vaso-vasostomy on 1 side in dog No. 21 using technique IV following severe infection and suppuration. In the remaining 81 studies there was primary healing. The results of radiographic and histopathological studies were correlated as far as possible.

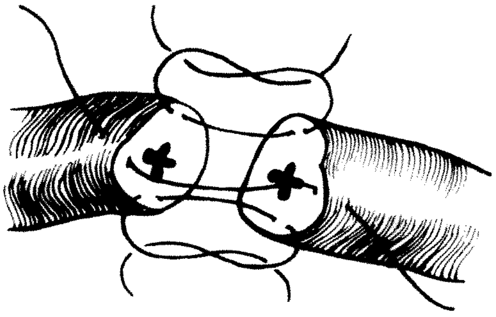


Fig. 1 Technique of end-to-end vaso-vasostomy without an internal splint.

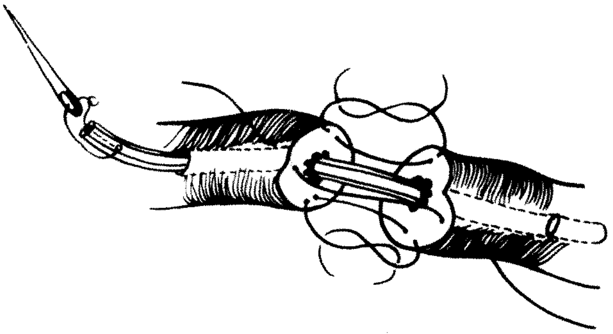
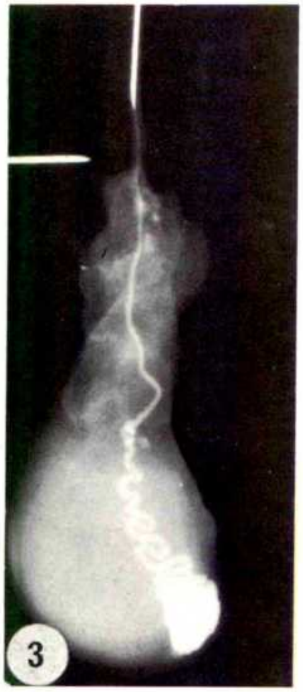
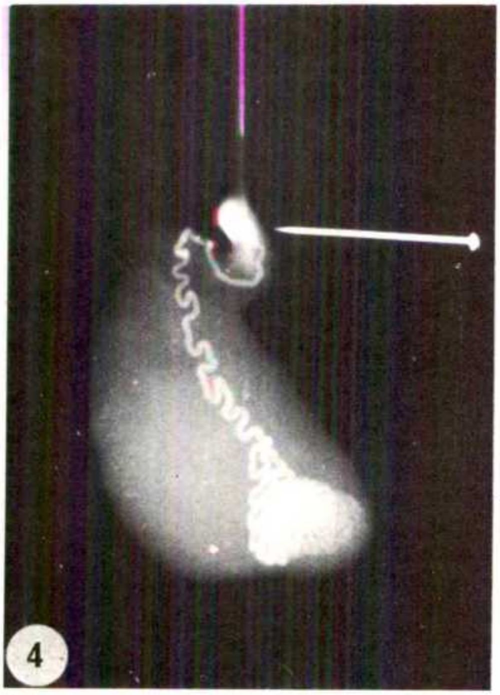


Fig. 2 End-to-end anastomosis with polythene tube as internal splint. The internal splint is attached to a needle and introduced from proximal to distal vas.





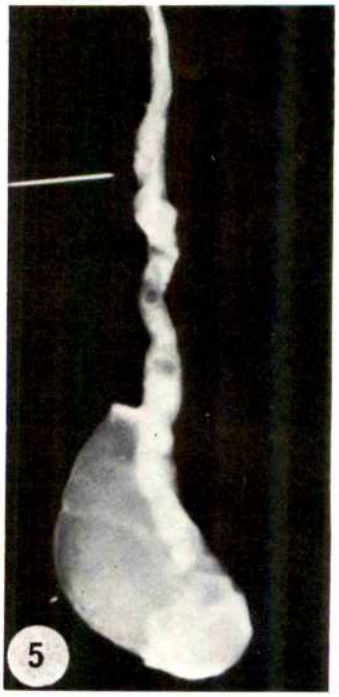


Fig. 3 Vasogram showing successful vaso-vasostomy.

Fig. 4 Vasogram showing patent anastomosis but marked extravasation of dye from the site of repair.

Fig. 5 Vasogram depicting a dilated and tortuous proximal vas deferens.

Radiographic Findings (Table 2)

After successful vaso-vasostomy, the contrast medium was visualised as a thin line extending along the proximal vas and epididymis as a convoluted tube up to the lower pole of the testis (Fig. 3). There was some pooling of dye or leakage at the site of anastomosis in 1 specimen (Fig. 4).

Using techniques I and II, 15 out of 20 anastomoses were patent and 14 of these were confirmed by histology. With techniques III and IV, only 5 out of 22 vasa were patent. This difference was highly significant ($\chi^2 = 11.48$, $P < 0.001$). The results were better when polythene tubing (00) was used as the internal splint (IIIa and IVa) because 4 out of 12 vasa were patent compared with 1 out of 10 vasa in which a 2/0 nylon splint was used (techniques IIIb and IVb). However, the difference between the 2 internal splints was not significant ($\chi^2 = 1.691$, $P > 0.05$).

The overall results in group I revealed a radiographic success in 20 vasa, although another 9 were patent on microscopic examination only (Table 3). In 5 of the latter the vasography was unsuccessful because of technical problems. However, all of these were regarded as failures.

In group II, 24 out of the 40 vasa deferentia were patent on radiography and another 12 were patent by microscopy only. Comparison of the overall results of group I primary repair versus

Table 2 Successful Results According to Technique

Technique	*Group I*	*Group II*	*Total*
Without internal splint	15/20	14/20	29/40
With internal splint (polythene tube)	4/12	6/10	10/22
With internal splint (nylon 2/0)	1/10	4/10	5/20
Combined results of splints	5/22	10/20	15/42

Table 3 Results of Vaso-Vasostomy

Result	*Group I*	*Group II*
Number of vasa	42	40
Successful vaso-vasostomy:		
Radiography only	20	24
Radiography + histology	19	24
Histology only*	9	12
Leakage from anastomosis	24	18

* These were regarded as failures and excluded.

Table 4 Changes in the Vas Deferens

Pathological changes	*Group I*	*Group II*
Inflammatory changes	23	17
Patent vas deferens	6	9
Non-patent vas deferens	17	8
Spermatic granuloma	7	1
Suture granuloma	11	16

Table 5 Correlation of Spermatogenesis to Results

	Normal spermatogenesis	
	Group I	*Group II*
Testicular biopsy	31	40
Post-operative histology	18*	10
Patent vaso-vasostomies	10	7
No splints	8	6
With internal splints	2	1

* One additional testis showed spermatogenesis in post-operative examination only.

secondary repair (group II) showed no significant difference ($\chi^2 = 1.263$, $P > 0.05$). The success rate with techniques V and VI (14 out of 20 anastomoses without splints) as compared to techniques VII and VIII (10 out of 20 anastomoses with internal splints) did not reveal any significant difference ($\chi^2 = 1.667$, $P > 0.05$). Similarly, there was no difference when the results of a hollow internal splint (6 out of 10 anastomoses) with polythene tube 00 were compared to a solid splint (4 out of 10 operations) with monofilament nylon 2/0 ($\chi^2 = 0.80$, $P > 0.05$). However, the combined results of groups I and II revealed a highly significant difference between the non-splinted and splinted anastomoses ($\chi^2 = 11.13$; $P < 0.001$).

Leakage

There was evidence of leakage from the site of anastomosis in 24 vasa of group I and 18 vasa of group II. There was gross leakage in vasa removed after 4 weeks. Leakage was also greater if the vas deferens was not patent. If the anastomosis was patent, leakage was less after the use of internal splints.

Pathological Findings

Vas deferens: A fusiform swelling was invariably seen at the site of vaso-vasostomy with adhesions to the surrounding structures of the cord. There were also signs of inflammation and fibrosis. In group II the proximal vas was dilated, tortuous and distended with a milky fluid. This dilatation was found in 23 vasa and demonstrable on inspection and vasography (Fig. 5).

Histological evidence of the presence of a lumen did not always correlate with radiographic findings. In the absence of serial sections across the site of anastomosis, only radiographic findings were relied upon (Table 3). The patency of the vas was correlated to the inflammatory changes in the vas (Table 4). In both groups inflammatory changes were minimal with a patent repair. This difference was highly significant in group I ($\chi^2 = 10.527$, $P < 0.005$), but not in group II ($\chi^2 = 1.0597$, $P > 0.05$). The inflammatory changes were more marked and extensive after the use of internal splints.

There were 7 spermatic granulomas, mainly with techniques I, II and III. Four of these were found with a patent vaso-vasostomy. In group II there was only 1 spermatic granuloma.

The difference between the 2 groups was not significant ($\chi^2 = 3.196$, $P > 0.05$).

Suture granulomas were found in 11 out of 42 operations in group I, and 16 out of 40 vasa in group II, but this difference was not significant ($\chi^2 = 1.769$, $P > 0.05$).

Epididymis: There was naked eye dilatation of the epididymis. The epididymal ducts showed dilatation on microscopic examination in 14 out of 40 vasa in group II. Dead spermatozoa and macrophages could be seen in these dilated ducts.

Testis (Tables 5 and 6): The testicular histology on initial biopsy was compared with the histology of the same testis excised 6 weeks after vaso-vasostomy.

Normal spermatogenesis was found in 18 out of 31 testes in group I and one-quarter (10/40) of the testes in group II. This difference was highly significant ($\chi^2 = 7.971$, $P < 0.005$). Correlation of

Table 6 Changes in the Testes

Pathological findings	*Group I*	*Group II*
Spermatogenesis and infection	6	1
Inflammatory changes only	8	4
Focal necrosis	3	6
Atrophy of testes	10	12 (4)*
Suture granulomas	7	2
Spermatic granulomas	0	2
Arrest of spermatogenesis	2	8

* Infarction of testis in 4 units.

spermatogenesis to successful vaso-vasostomy did not reveal any significant difference either in group I or group II, as well as the combined results of the 2 groups ($\chi^2 = 2.085$, $P > 0.05$).

In the majority of the testes, the absence of spermatogenesis could be attributed to infection leading to inflammation, haemorrhage, focal necrosis, atrophy and infarction of the testis following testicular biopsy. There was infarction of the testis in 4 vasa using technique VI, probably due to injury to testicular blood vessels at the second operation. The incidence and degree of inflammatory changes were more marked in splinted anastomoses. There was arrest of spermatogenesis of unexplained aetiology in 10 vasa.

Discussion

Various techniques for vaso-vasostomy have undergone evaluation in the experimental laboratory during the past 15 years (Schmidt, 1956, 1959a and b, 1961 and 1975; Moon and Bunge, 1967; Fernandes *et al.*, 1968; Gursel *et al.*, 1970). Most of these experimental studies have been carried out to translate the principles of microvascular surgery to the repair of the vas. The results obtained in the present study have confirmed the findings of previous workers.

The main objective of the present study was to confirm the choice of suture material and evaluate the need for internal splints, either solid or hollow. Fine, non-irritating sutures such as 6/0 silk, 6/0 Prolene or similar synthetic materials on small eyeless cutting needles are ideal for vaso-vasostomy as the vas has a narrow lumen but thick muscular walls.

The use of internal splints, either monofilament nylon 2/0 or polythene tube (00), gave poor results as compared to non-splinted repair in both series. In the initial stages of the work, a number of methods (Schmidt, 1959a and b; Dorsey, 1973) were tried to place the internal splints into the lumen of the vas. Since 2/0 nylon on eyeless needles was not available the monofilament nylon was anchored to a straight milliner's needle by fine silk. The polythene tubing (00) was very soft and could not be passed into the lumen of the vas. The placement of these splints was more difficult when there were inflammatory changes and fibrosis of the vas in secondary repair. The needle bearing these splints also stretched and injured the epithelial lining of the vas during repeated attempts at introduction. The splints were buried in the subcutaneous tissues but sometimes they were extruded if the dog pulled at his dressing.

The results with splinted anastomoses in group II improved after these technical difficulties were overcome. Although in group I the difference between non-splinted and splinted anastomoses was highly significant, in group II this difference was no longer significant. The presence of a splint caused severe inflammatory changes in the vas deferens and the epididymis with fibrosis even when the anastomosis was patent. There was evidence of leakage and spermatic granulomas at the site of lateral holes in the vas through which the splint was brought out. Although the difference between monofilament nylon or polythene tube was not significant, the results were better with a hollow splint (polythene tube) quantitatively as well as qualitatively.

Earlier workers, including O'Conor (1961) and Phadke and Phadke (1967), have advocated the use of an internal splint (preferably a hollow tube) to ensure proper alignment of the lumen, to provide a tract for rapid epithelisation and to divert the spermatic fluid with a view to avoiding leakage and the formation of spermatic granuloma. However, based on the experience of others as well as our own experience in dogs, the disadvantages of an internal splint may be summarised:

1. The splints may be difficult to introduce and cause trauma to the mucosa of the vas.
2. The splints are difficult to maintain in their proper place, especially in dogs, because of the narrow lumen, and there is danger of extrusion.
3. There is irritation of the vas leading to foreign body reaction, inflammation, fibrosis and obliteration of the lumen of the vas and epididymis.
4. There may be leakage at the site of puncture where these splints pierce the wall of the vas deferens, leading to infection and spermatic granuloma.
5. The splint acts as a route for infection.

In the light of these observations, the use of these splints has been abandoned by Schmidt (1975) and Fernandes *et al.* (1968). An end-to-end mucosa-to-mucosa anastomosis using 6/0 silk or Prolene sutures placed under magnification by means of a binocular operating microscope or magnifying loupe provides an accurate, leak-proof repair. This is a simple method and ensures a high success rate.

There was a relatively high incidence of leakage and spermatic granuloma in the early stages of this work. However, with experience and greater precision, these problems were minimised.

The present study failed to elucidate the reasons for the high failure rate of spermatogenesis after vasectomy. It was difficult to maintain proper asepsis and avoid infection in these dogs despite all precautions. Haemorrhage, focal necrosis and infection with abscess formation at the site of testicular biopsy would account for a few instances of atrophy and absence of spermatogenesis. Normal spermatogenesis might have returned if these testes had been allowed to remain for a longer interval. It might be safer to avoid a testicular biopsy at the time of vaso-vasostomy on human beings. There is a need for long-term studies on testicular function after vasectomy and recanalisation.

It is concluded that end-to-end mucosa-to-mucosa vaso-vasostomy using interrupted sutures of either 6/0 silk or Prolene on small cutting eyeless needles introduced under magnification and without any internal splints gives the best results. There is a need for more long-term studies to determine the effects of vasectomy on spermatogenesis which accounts for some of the failures after successful recanalisation.

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Orchiopexy in the Prune Belly Syndrome

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Summary—It has been suggested that abdominal testes might have better ultimate function if brought to the scrotum at a very early age.

In a study of 16 patients with the prune belly syndrome, 8 had reconstruction of the urinary tract together with an orchiopexy and 2 had an orchiopexy alone.

The results in these patients support the view that an orchiopexy in the neonate or young infant offers the best chance of obtaining viable testes in the scrotum.

In undescended testes the ultimate potential for function, especially spermatogenic, remains a mystery. While the trend has been towards earlier orchiopexy for preservation of function, the optimal age for operation is still controversial. For inguinal or subcutaneous testes the timing of surgery may, in fact, make little difference. However, for intra-abdominal testes there is some evidence to suggest that preservation of function might best be served by orchiopexy done during early infancy (Charny, 1960; Myers and Kelalis, 1973; Dougall *et al.*, 1974; Lattimer *et al.*, 1974).

The prune belly syndrome is characterised by the triad of deficient abdominal musculature, undescended (intra-abdominal) testes and dilatation of the urinary collecting system. The early mortality has exceeded 50%. While recent data indicate an improved survival for individuals with prune belly syndrome, reports of successful orchiopexy in these patients have been uncommon. The magnitude of the urinary tract abnormality and its complications has apparently overshadowed consideration of the cryptorchidism, resulting in the orchiopexy being either delayed or omitted. In such an orchiopexy the major technical problem, namely insufficient length of the spermatic vessels, has been overcome in a few instances by either dividing those vessels or performing a staged operation (Williams and Burkholder, 1967; Burke *et al.*, 1969; Waldbaum and Marshall, 1970; Welch and Kearney, 1974; Woodard and Parrott, 1977).

Our approach to infants with prune belly syndrome, including management of the cryptorchidism, has been aggressive (Woodard and Parrott, 1977). With the hope that the operation would be technically more satisfactory at an earlier age, in our most recent patients afflicted with this syndrome orchiopexy was performed in the first 6 months of life, in combination with major urinary reconstructions. These results were compared with those achieved by "standard"

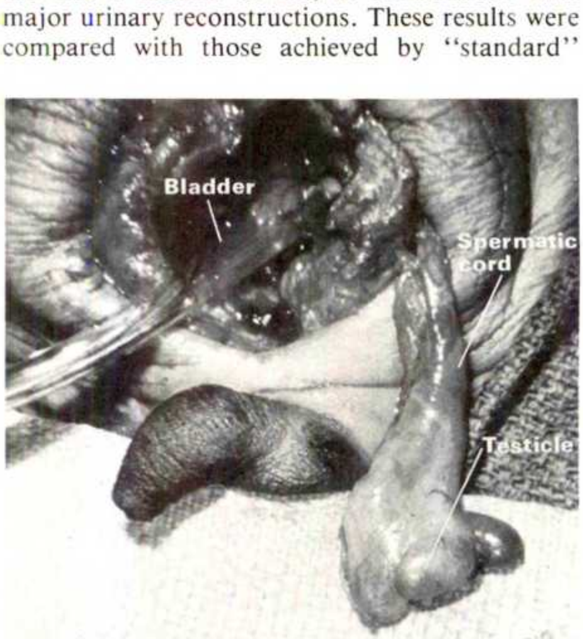

Fig. 1 Intra-operative photograph showing length of intact spermatic cord relative to scrotum during orchiopexy combined with extensive ureteric tailoring in Patient No. 6 (J.W.).

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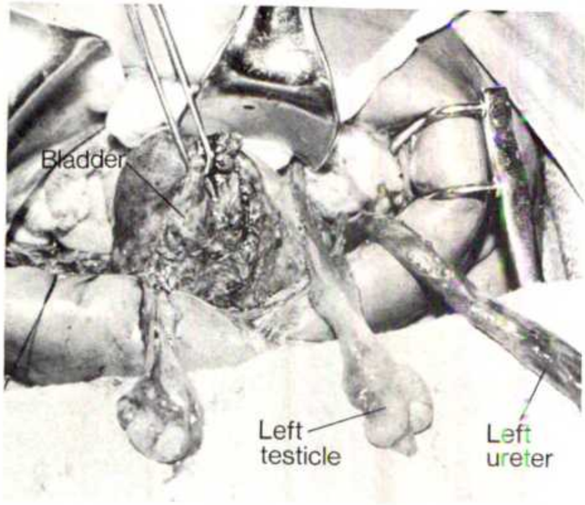

Fig. 2 Intra-operative photograph showing length of spermatic cords in relation to the ureter during neonatal orchiopexy combined with ureteric tailoring in Patient No. 8 (K.E.).

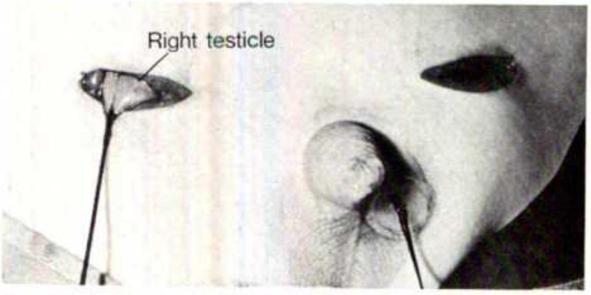

Fig. 3 Photograph at the end of operation on Patient No. 2 (G.W.) having transabdominal orchiopexy not combined with ureteric tailoring at the age of 3 years. Right testis would reach no further than the external inguinal ring while left testis reached the upper portion of the scrotum.

transabdominal orchiopexy in the older prune belly child.

Patients and Methods

Since 1969, 16 new patients with prune belly syndrome have been evaluated and treated by the authors at The Henrietta Egleston Hospital for Children. Ten of these have had severe uropathy but sufficient renal parenchyma to allow total urinary reconstructive procedures. These 10 form the basis of this report. Their ages on admission ranged from 1 day to 6 years. Of the 8 who were neonates, 7 had extensive reconstruction of their urinary tracts during the first 6 months of life. Orchiopexy, unilateral or bilateral, was performed at the time of urinary reconstruction (Figs. 1 and 2). Of the 3 other patients, 2 underwent bilateral transabdominal orchiopexy, not associated with urinary reconstruction (Fig. 3), at the ages of 5 and 7 years. The final patient (J.D.), treated initially by loop cutaneous ureterostomy, later underwent unilateral orchiopexy during a subsequent urinary reconstruction. In all of the 10 cases operation revealed the testes to be overlying the ureters in the pelvis (Fig. 4) and transabdominal exposure was deemed a necessity. In most instances dissection of the underlying ureter facilitated mobilisation of the spermatic vessels as far proximally as the lower pole of the kidney. The testicle was then brought into the scrotum by perforating the medial wall of the inguinal canal at the external ring.

Results

The present status of the testes in each case is shown in Table 1. A total of 17 testes in these 10 patients has been subjected to orchiopexy. Because of insufficient spermatic vascular length at the initial operation 6 testes either never reached the scrotum completely or retracted into the groin after having been placed in the scrotum. Two second-stage procedures have been successful. A total of 14 testes now reside without atrophy in the scrotum.

If a good result may be defined as the achievement of at least 1 scrotal testis without atrophy following unilateral or bilateral orchiopexy, good results were obtained with 1 operation in all cases where orchiopexy was combined with neonatal or early infantile urinary reconstructions. On the other hand, only 1 of 3 children undergoing delayed orchiopexy had good results with a single operation. Testis biopsy, done in only 1 case, revealed immature testicular tissue with a fibrous tunica albuginea and immature but structurally preserved tubules.

Discussion

Failure of testicular descent in patients with prune belly syndrome is such a characteristic feature that any exception to this must make the diagnosis doubtful. The testes in all of our 10 patients were found in the pelvis overlying the

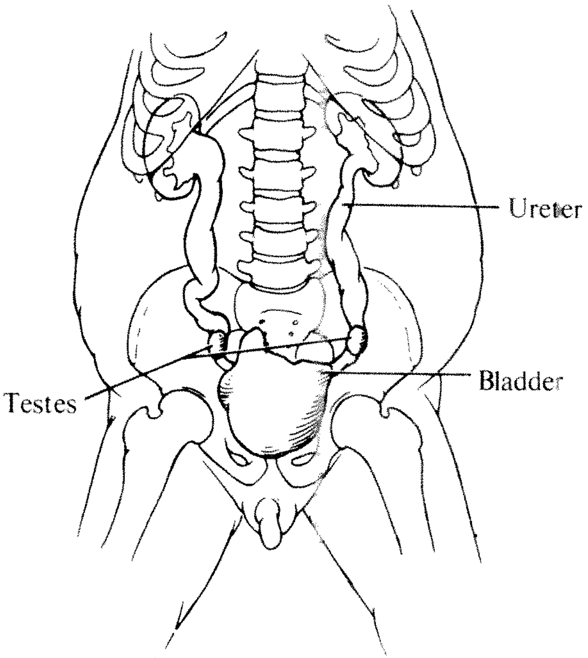

Fig. 4 Diagram showing typical location of intra-abdominal testes in patients having prune belly syndrome.

ureters at about the sacro-iliac level (Fig. 4). Lattimer (1958) commented that the testes were commonly attached to the mid-ureter. As in the necropsy cases of Nunn and Stephens (1961), all testes in our cases were small, intra-abdominal and lifted off the abdominal wall by enlarged ureters. Several were near the ureterovesical junction and only 1 had descended as far as the internal inguinal ring. In the report by Grossman *et al.* (1970) all testes subjected to orchiopexy were intra-abdominal, while Williams and Burkholder (1967) found them lying on the anterior surface of the ureters low in the pelvis.

The cause of cryptorchidism in these patients remains unknown. An early theory postulating obstruction to testicular descent by a dilated urinary tract is refuted by the usual absence of cryptorchidism in patients with similarly dilated urinary systems resulting from bladder outlet obstruction such as that caused by posterior urethral valves. Williams and Burkholder (1967) considered the cryptorchidism to be secondary to the abdominal wall defect while Nunn and Stephens (1961) suggested that an intrinsic abnormality of the testis prevented its descent. However, in 1 of the few reports in which testicular histology is mentioned, Nunn and Stephens' (1961) review of testicular tissue obtained at necropsy revealed testes that were small but histologically normal for the age of the patient.

Paternity has not been reported in patients with the prune belly syndrome but adequate testosterone production was evident in two-thirds of Nunn and Stephens' older patients and in 1 of McGovern and Marshall's (1959). There is also evidence of ejaculatory potential in persons having this syndrome (Stephens, 1976).

In the English language literature, reports were found of only 18 attempts at orchiopexy. Lattimer (1958) merely mentioned the procedure, Williams and Burkholder (1967) reported success with a 2-staged orchiopexy in 4 patients, while Grossman *et al.* (1970) reported attempts in 3 patients with

Table 1 Data on 10 Consecutive Patients with Prune Belly Syndrome who Underwent Orchiopexy

	Patient	*Age at presentation*	*Present age*	*Age at right orchiopexy*	*Age at left orchiopexy*	*Present status*		*Urological status*
						R	*L*	
1.	J.D.	6 years	11 years	-	6 years	-	pub. tubercle*	Total late reconstruction
2.	G.W.	3 years	6 years	5 years	5 years	groin†	scrotal	Total late reconstruction
3.	T.T.	newborn	7 years	7 years	7 years	groin*	scrotal	Staged early reconstruction
4.	I.S.	newborn	4 years	1 month	6 months	scrotal	scrotal	Staged early reconstruction
5.	D.M.	newborn	4 years	4 months	-	scrotal	-	Staged early reconstruction
6.	J.W.	newborn	1 year	-	1 month	-	scrotal	Total early reconstruction
7.	M.B.	newborn	7 months	5 months	5 months	groin	scrotal	Bilateral neonatal pyeloplasty and early reconstruction
8.	K.E.	newborn	5 months	1 month	1 month	groin	scrotal	Total early reconstruction
9.	D.B.	newborn	2 months	2 weeks	2 weeks	scrotal	scrotal	Total early reconstruction
10.	K.H.	newborn	1 month	2 weeks	2 weeks	scrotal	scrotal	Total early reconstruction

* Now scrotal after second-stage orchiopexy.

† Atrophic testis removed at second-stage orchiopexy attempt.

Table 2 Results of Orchiopexy in 10 Consecutive Patients with Prune Belly Syndrome who Underwent Orchiopexy

Time of orchiopexy	*Number of patients*	*Good result*	*Poor result*
Neonatal or early infancy combined with ureteric tailoring	7	7	0
Later transabdominal or inguinal	3	1	2

success after 1 operation in a single case. In 3 older children, Barnhouse (1972) divided the spermatic vessels to obtain adequate length, apparently without subsequent testicular atrophy. Welch and Kearney (1974) reported orchiopexy in 8 patients, the youngest being 9 months of age. While they gave no indication of the degree of success, they recommended that orchiopexy be an integral part of the rehabilitation of these patients and suggested that it should be carried out in stages around the age of 3 to 5 years. Analysis of these reported series revealed that orchiopexy in older children with prune belly syndrome resulted in only a small percentage of the testes reaching the scrotum in a single operation without dividing the spermatic vessels. While our experience with older children was somewhat similar, orchiopexy performed during the ureteric straightening in neonates or young infants easily allowed for sufficient cord length without dividing the testicular vessels and without atrophy. Retraction subsequently occurred in 2 instances, but never bilaterally.

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The Authors

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Requests for reprints to: John R. Woodard, Emory University Clinic, 1365 Clifton Road, N.E., Atlanta, Georgia 30322, USA.

British Journal of Urology (1978), **50**, 352

Case Reports

Antisperm Antibodies in a Case of Secondary Unilateral Testicular Atrophy

Case Report

A 19-year-old male presented with a history that 9 months previously he had had fever, with swelling and pain in the right testis and epididymis which subsided within 2 weeks. On examination the right testis was considerably reduced in volume and of firm consistency, the epididymis was not palpable. The left testis was normal. The seminal analysis was abnormal (see table). Agglutinating, immobilising and cytotoxic antisperm auto-antibodies tests revealed positive sperm cytotoxic auto-antibodies both in the blood serum and seminal plasma (Rose *et al.*, 1976).

Right orchidectomy was performed and histological examination demonstrated mostly tubular ghosts; a few tubules were markedly reduced in volume and the tubular walls were significantly thickened; only rare cells of the germinal epithelium were seen, but there was diffuse infiltration of lymphatic cells in the interstitial tissue. At follow-up the spermiocytotoxic auto-antibodies were seen to gradually decrease until complete disappearance, and seminal fluid returned to normal (see table).

Comment

The presence of an auto-immune orchitis in animals has been amply demonstrated. Clinical findings have revealed an autoimmune infertility in men due to antisperm auto-antibodies, and much controversy exists regarding success of therapy in these patients (Shulman, 1975). In our opinion, the case described appears to indicate the possibility of antisperm auto-immunisation due to a previous testicular lesion, with subsequent self supporting perpetuation of the lesion and severe dyspermia. Removal of the testis initially affected broke the antisperm auto-immune reaction, thus enabling physiological spermiogenesis to take place in the other testis.

References

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Schulman, S. (1975). Reproduction and Antibody Response. 1st edn., pp. 94-95, Cleveland, Ohio: CRC Press.

The Authors

C. Laurenti and A. Fagioli, Department of Urology, Rome University, Italy.

A. Lenzi and F. Dondero, II Medical Pathology, Department on Internal Medicine, Rome University, Italy 00100.

Table Unilateral-Orchidectomy

	Sperm agglutinating antibodies		*Sperm immobilising antibodies*		*Sperm cytotoxic antibodies*		*Seminal parameters*		
	Serum	*Semen*	*Serum*	*Semen*	*Serum*	*Semen*	*Spermatozoa number/ ejaculate*	*Sperm motility (2nd h)*	*Aberrant forms*
Basal	Neg.	Neg.	Neg.	Neg.	1/16	1/64	36,000,000	5%	35%
After 3 months	Neg.	Neg.	Neg.	Neg.	1/8	1/16	61,000,000	5%	32%
After 6 months	Neg.	Neg.	Neg.	Neg.	1/4	1/4	160,000,000	40%	21%
After 9 months	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	276,000,000	50%	18%

British Journal of Urology (1978), **50**, 353

Inversion of the Urinary Bladder

Inversion of the urinary bladder is an extremely rare condition. A review of the literature does not report a single case to our knowledge. Herniation of the bladder into the scrotum and into the sac of inguinal hernia has, however, been reported even though these are rare (Soloway *et al.*, 1960).

Case Report

Mrs M.N., aged 55 years, was admitted with a history of sudden appearance of a "lump at the vulva" while lifting a heavy weight. This was accompanied by severe lower abdominal pain. She had had 4 children and the deliveries were apparently normal.

IVP showed bilateral hydroureters and commencing hydronephrosis on the left side. The bladder outline was not visualised. At examination under anaesthesia the urethral orifice could not be located. The "lump" (Fig. 1) protruded through a tight ring of about 2 cm in diameter and close scrutiny of its ventral aspect revealed the 2 ureteric orifices (Fig. 2). During the repair procedure, reduction was accomplished, but the patient unfortunately had a cardiac arrest and died 24 h later.

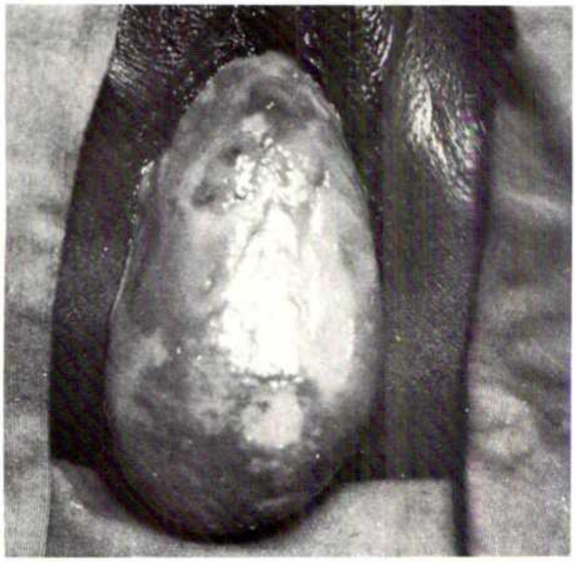
Fig. 1

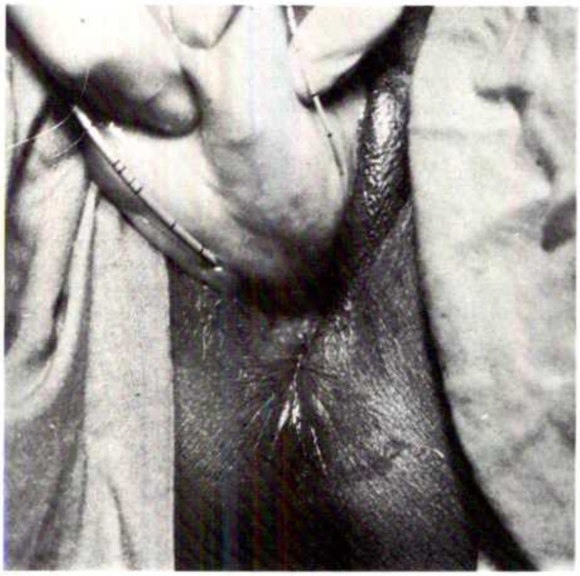
Fig. 2

Comments

Inversion of the urinary bladder is a rare occurrence. The initial diagnosis in this case was an "incarcerated utero-vaginal prolapse". Suspicion of an inverted bladder first arose when attempts at catheterisation failed, because the urethral orifice could not be identified. Subsequently at examination under anaesthesia, the diagnosis was confirmed, when the ureteric orifices were located on the ventral aspect of the "lump". We are unable to find any aetiological factors, which caused the inversion except for the fact that she is multiparous and post-menopausal and the inversion followed lifting a heavy weight.

References

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The Authors

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British Journal of Urology (1978), **50**, 354

Absent Dartos

Case Report

A 32-year-old patient presented with primary sterility for 10 years. Semen examination showed high volume (8 ml) and severe oligozoospermia (1.5 million per ml). All sperms were deformed and non-motile. The patient had normal thyroid, adrenocortical and pituitary gonadotropin function test results. All the known causes of male infertility as outlined by Dubin and Amelar (1971) were excluded.

The scrotal skin was very thin, redundant and showed some longitudinal folds but no transverse rugae. It did not react to hot or cold sponging. The cremasteric reflex was weak on both sides. The testicles were normal in size but soft. The epididymis and spermatic cord were normal. Testicular biopsy showed degeneration of cells lining seminiferous tubules with occasional maturation into spermatids.

Exploration revealed normal intrascrotal structures. Cremasteric and scrotal skin biopsies, stained with haematoxylin and eosin and Verhoeff-van Gieson, showed normal cremaster and absent dartos.

Comment

A reference to absent dartos could not be traced in the literature. The criteria of diagnosis comprise a thin non-reactive scrotal skin and an absent dartos on biopsy.

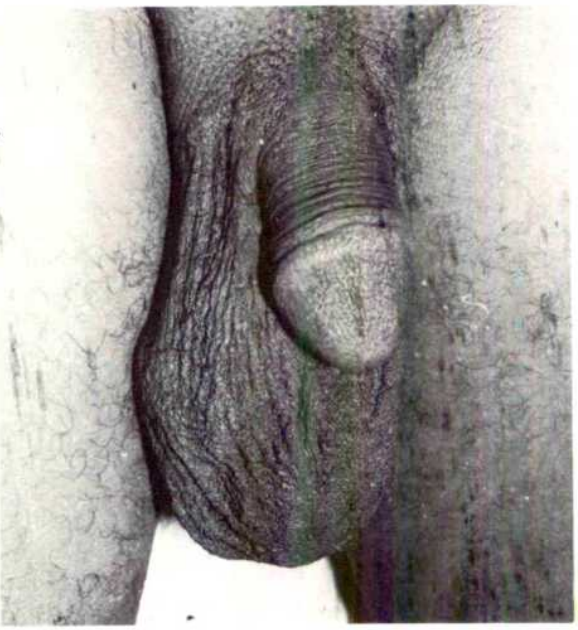

Fig. 1

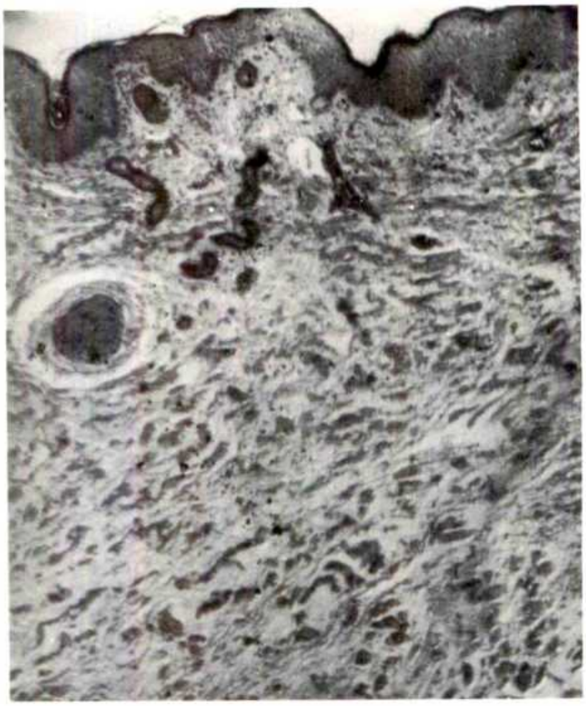

Fig. 2

The dartos plays a significant role in testicular thermoregulation (Shafik, 1973). A constant scrotal-rectal temperature difference under varied environmental temperature is maintained by a cremasterico-dartos synchronous action mediated through the scrotal ligament (Shafik, 1977). Absent dartos may interfere with this mechanism and disturb spermatogenesis.

References

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The Author

Ahmed Shafik, Professor of Surgery, Faculty of Medicine, Cairo University, Cairo, Egypt.

British Journal of Urology (1978), **50**, 355

Leukoplakia of the Penis—Bleomycin Treatment

Case Report

A 54-year-old male presented with painless induration of the glans penis. He had not been circumcised. Dorsal incision of the prepuce revealed leukoplakia of almost all of the area inside the prepuce and a quarter of the glans, which were covered with white-grey coat (Fig. 1).

Because local complete excision of the leukoplakia lesion including the glans penis would bring about disturbance in his sex life, a total of 135 mg of Bleomycin was given intravenously and 0.5% Bleomycin ointment was applied on the incision scar and the lesion of the glans penis, after the lesion was excised as extensively as possible (Fig. 2).

A 3 year follow-up showed no recurrence and no disturbance in his sex life.

Comment

In the standard textbook *Urology*, in addition to local excision, amputation of the penis is mentioned as a possible mode of treatment (Campbell and Harrison, 1970). Intravenous medication of Bleomycin and local application of the same drug as an ointment on the incision scar and the residual lesion of the glans penis brought about good results.

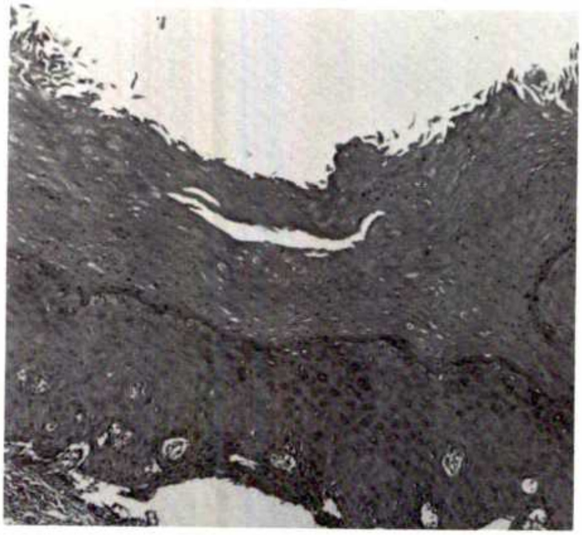

Fig. 2 Hyperkeratosis, parakeratosis, and hypertrophy, hyperplasia of prickle-cell layer with oedema and lymphocytic infiltration in the dermis.

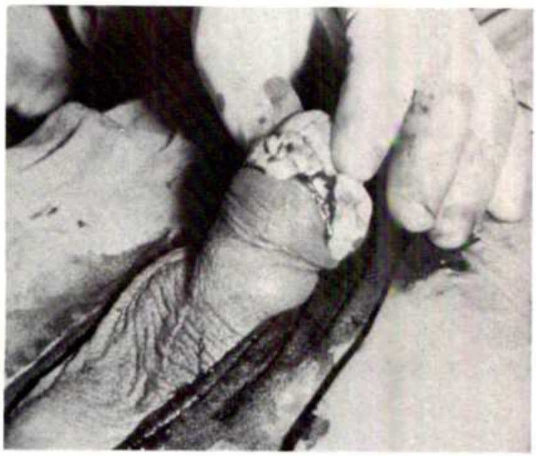

Fig. 1

Reference

Campbell, M. F. and Harrison, J. H. (1970). *Urology,* 3rd edn., Philadelphia: W. B. Saunders Company, **1**, 524-525 and **2**, 1192.

The Authors

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British Journal of Urology (1978), **50**, 356

Exstrophy-Variant of the Bladder

Case Report

A 21-year-old African female presented with a 2 year history of enuresis, urgency, urge incontinence and a poor stream. Physical examination revealed a distended bladder, low set umbilicus, minimal pubic hair, and normal genitalia (Fig. 1). Urine culture showed a significant growth of *E. coli*. On excretory urography both kidneys appeared normal, but both ureters were dilated. Cystogram showed fairly wide separation of the pubic bones, a trabeculated, sacculated bladder with a large diverticulum and large post-micturition residual volume (Fig. 2). Cystoscopy revealed a stenosed bladder neck. She was treated with appropriate antibiotics and urethral dilatation, and immediately became totally asymptomatic for the first time in 2 years.

Comment

This is a rare variant of the bladder exstrophy-epispadias complex. By 1971 only 9 cases had been reported (Ignatoff *et al.*, 1971) and since then no further cases could be found in the literature. This represents only the second case presenting as a bladder outlet obstruction, the others having no functional impairment of the lower urinary tract (Uson and Roberts, 1958). The starting point in all varieties of the exstrophy-epispadias complex is believed to be an abnormally persistent or overdeveloped cloacal membrane (Marshall and Muecke, 1962).

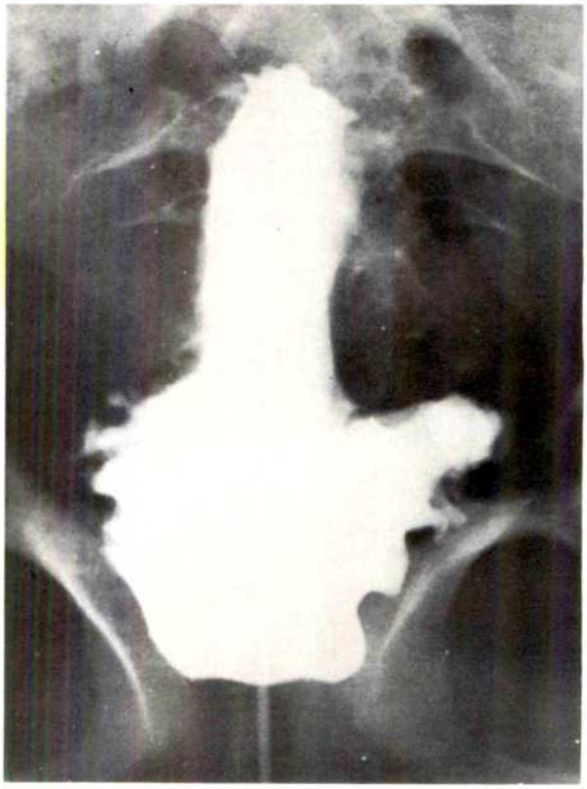

Fig. 2

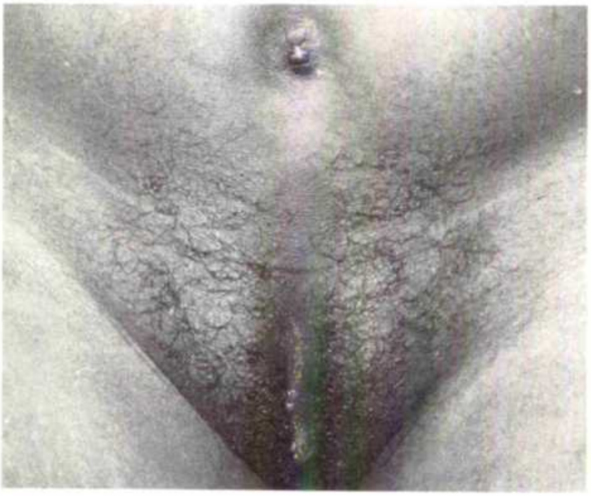

Fig. 1

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British Journal of Urology (1978), **50**, 357

Both Ureteric Orifices on the Same Side of the Bladder

Case Report

A 2-year-old girl was admitted to hospital for investigation for failure to thrive. She was mentally retarded but had normal control of micturition by day. She had blue sclera. Her urine was infected with *E. coli*. An IVP showed a normal right upper urinary tract, but on the left there was a moderate degree of hydroureter. An MCU showed left vesico-ureteric reflux with dilatation of the ureter.

At operation (Fig.) the right ureteric orifice lay at the site normally occupied by the left ureteric orifice. The left ureter which was moderately dilated, looped upwards and entered the bladder high on its left lateral wall. Both ureters were mobilised and reimplanted by the Glenn Anderson cross-over technique, the left ureter being led into the bladder via the hiatus previously occupied by the right ureter and the right ureter via a new hiatus low on the right side of the bladder. The patient made an uneventful recovery and an IVP 6 months post-operatively showed normal upper urinary tracts.

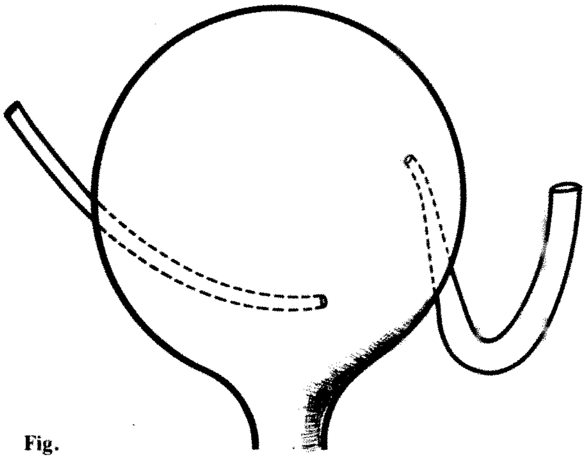

Fig.

Comment

Although this patient could be described as having ectopic ureters, these in no way resembled the normal types of ureteric ectopia which are readily explicable on an embryological basis (Williams, 1974). In this case it would seem that early embryogenesis proceeded normally, but that the trigonal area of the bladder subsequently twisted to the left in later foetal development; it is interesting to note that this process did not disturb the bladder neck mechanism.

Reference

Williams, D. I. (1974). Ectopic ureter. *Encyclopedia of Urology,* Supplement XV, Berlin: Springer-Verlag.

The Author

A. M. K. Rickwood, The Children's Hospital, Western Bank, Sheffield S10 2TH.

British Journal of Urology (1978), **50**, 358

Prostatic Adenocarcinoma with Ectopic ACTH Production

Case Report

A 76-year-old man, previously fit, presented with hypomania. He had gross bilateral leg and ankle oedema, but did not look Cushingoid. BP 220/110.

Investigations

Fasting blood sugar: 260 mg% with glycosuria. Electrolytes: Na = 149; K = 2.4; HCO_3 = 40 mEq/L. Blood cortisol levels (9 a.m. and midnight): over 100 μg/100 ml; "extremely high levels compatible only with a site of ectopic ACTH production". Chest X-ray: no evidence of neoplasm.

His hypomanic state regressed, he became comatose and died before further investigations could be made, 4 weeks after the onset of his illness.

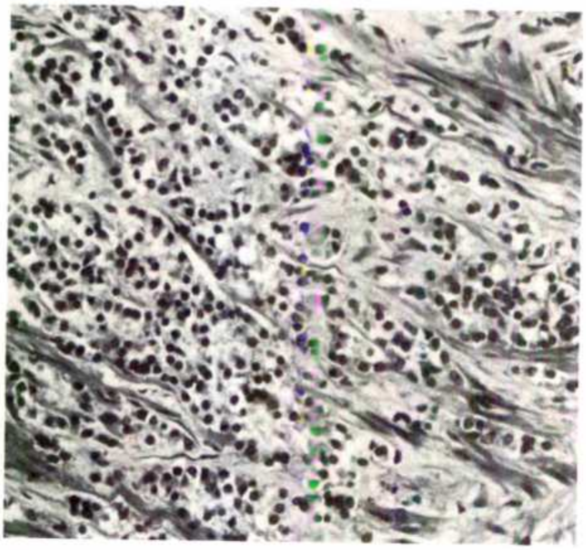

Fig. Prostate. Infiltrated by poorly-differentiated adenocarcinoma. (H and E × 200.)

Post-mortem findings

The prostate was not enlarged but microscopy showed widespread infiltration by poorly-differentiated adenocarcinoma (Fig.). Tumour was invading the capsule but there were no metastases. No argentaffin or argyrophil granules could be demonstrated in it and the material was too autolysed for examination in the transmission electron microscope. Careful examination failed to reveal the presence of any other tumour. The adrenals were hyperplastic (20G) with total lipid depletion. Basophilic cells in the anterior lobe of the pituitary showed Crooke's hyaline change.

Comment

This case fulfils the criteria needed to establish a causal relationship between prostatic carcinoma and ectopic ACTH Cushing's syndrome (Azzopardi and Williams, 1968). Three similar cases have been previously discussed (Wenk *et al.*, 1977).

References

Azzopardi, J. G. and Williams, E. D. (1968). Pathology of "non-endocrine" tumours associated with Cushing's syndrome. *Cancer,* **22**, 274-286.

Wenk, R. E., Bhagavan, B. S., Levy, R., Miller, D. and Weisburger, W. (1977). Ectopic ACTH, prostatic oat cell carcinoma and marked hypernatremia. *Cancer,* **40**, 773-778.

The Authors

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British Journal of Urology (1978), **50**, 359

Book Reviews

Dialysis, Transplantation, Nephrology. Proceedings of the European Dialysis and Transplant Association. Edited by H. B. Robinson, J. B. Hawkins and P. Vereerstraeten. Volume 14. Pp. 660. Tunbridge Wells: Pitman Medical Publishing Co. Ltd. £18.00.

The Proceedings, now in its fourteenth edition, has a well deserved place as the standard annual reference in dialysis and transplantation in Europe. As usual, the volume begins with the useful Statistical Reviews and these now include an interesting section on the increasing proportion of children receiving replacement treatment. There is a special feature on the prospects for specific immunosuppression in transplantation and there is wide coverage on problems related to dialysis and transplantation. The large section on nephrology emphasises the relatively small surgical contribution in this field and the declining interest in preservation techniques. This is a very useful book for anyone interested in chronic renal failure and replacement methods.

Renal Nursing. Robert Undall. Second edition. Pp. 261. Oxford, London and Edinburgh: Blackwell Scientific Publications, 1977. £5.80.

The first edition of Robert Undall's paperback on renal nursing was an invaluable asset to nursing staff interested in renal disease. In this, the second edition, the information has been completely revised and updated. The information given is mainly related to practical renal nursing, but has a theoretical background to ensure complete understanding of the basic principles.

The book opens with a chapter on normal renal function. A brief outline is given of the anatomy of the kidney and its function. The following chapter explains tests and investigations necessary in renal disease. The main kidney diseases are then described, including diagnosis and management. This is followed by a discussion on acute and chronic renal failure, with details of aetiology and management.

The sections on peritoneal dialysis and haemodialysis give detailed descriptions of the various procedures and their complications. There are good clear diagrams to illustrate the text. The prevention of hepatitis is considered.

A new chapter is devoted to the management of poisoning. It includes both the conservative methods of treatment and haemodialysis.

Transplantation is fully described, including tissue typing, surgery, immunology and rejection. The book concludes with an appendix on dietary information and another on the preparation of peritoneal dialysis solution.

Although it probably does not give sufficient in-depth information for those specialising in renal disease, it should certainly give a firm foundation on which to build. Its inclusion in a School of Nursing library and its use at ward level for teaching are highly recommended.

Atlas of Gray Scale Ultrasonography. Kenneth J. W. Taylor. Pp. 411. Edinburgh: Churchill Livingstone, 1978. £19.50.

At a time of rapid advances in medical ultrasonics the author must be congratulated on producing this Gray Scale Atlas containing illustrations of such consistently high standard and excellent presentation. Admittedly much of the work has been produced on purpose-built equipment, but while pioneering gray scale technology and imaging during recent years Dr Taylor has accumulated enough first class material to enable him to publish at this most opportune time when commercial machines capable of giving comparable results are now becoming universally available to practitioners with the necessary expertise to use them.

For those of us who have persevered for years with bi-stable (black and white) images it is encouraging to witness in this book a revolution in resolution. For novices, the associated line drawings, anatomical orientation figures and brief explanatory texts help to clarify the many sonograms. Bibliography is perhaps understandably limited and on too many pages it is disappointing to see so much unused space.

The section on the urinary tract covers the subject adequately and the examples illustrate the scope of sonar in this field, especially in relation to other diagnostic modalities for the investigation of renal mass lesions and the non-functioning kidney. Urologists with access to ultrasound facilities will already be aware of its potential benefits but surely cannot fail to be impressed by the anatomical detail achieved in many of the illustrations. However, while the atlas may provide a useful reference for the surgical trainee, it is hardly an essential addition to the urological bookshelf. By contrast, it represents good value for money to the diagnostician with an ultrasonic interest.

British Journal of Urology (1978), 50, 360

Conferences and Courses

International Conference on Urinary Calculi

Perth, Western Australia. 4-8 August 1979.

The Conference will include sessions on: Theories of Stone Formation, The Epidemiology of Stone Diseases, Metabolic Inter-relationships, Medical and Surgical Treatment, Prevention of Stone Formation.

Further information from: Assoc. Professor J. G. Brockis, International Conference on Urinary Calculi, University Department of Surgery, Royal Perth Hospital, Box X2213, G.P.O., Perth, Western Australia 6001.

Edinburgh Urological Festival

Edinburgh. 4-6 September 1978.

A postgraduate course in urology for consultants, senior registrars and registrars. Main topics: Bladder tumours, Infertility, Urinary diversion and replacement, Prostatic disease and Antibiotics.

Further particulars from: Urological Festival Secretary, Department of Surgery, University Medical School, Teviot Place, Edinburgh EH8 9AG.

International Society for Cryosurgery

This Society was established in 1974 to foster the continued development and application of cryosurgery for the controlled cryogenic destruction of abnormal tissues.

An International Congress is held every third year where the latest results from all interested disciplines are presented and discussed.

Applications for membership from the Society's Secretary: Dr Marco Laudi, Via Nizza 39, 10125 Turin, Italy.

Request for Informal Proposals on Contraceptive Research and Development

The Program for Applied Research on Fertility Regulation (PARFR) at Northwestern University, Chicago, Illinois, is soliciting informal proposals from foreign and United States institutions for *Applied Research* projects in the field of fertility control. Proposals incorporating new ideas, techniques, and procedures, with the objective of developing new or improved methods of fertility control appropriate for use in developing countries will receive priority consideration. PARFR's interest in contraception includes the full range of fertility control methods—hormonal and other pharmacologic agents, mechanical and surgical. Contraceptive methods proposed for research support should be close to the stage of clinical applicability, although projects could include laboratory, animal and/or human investigation.

Further information can be obtained by writing or calling: Director of Administration, Program for Applied Research on Fertility Regulation, 1040 Passavant Pavilion, 303 East Superior Street, Chicago, Illinois 60611, USA. Telephone: (312) 649-2990.

Society of Uroradiology. First Annual Course

New York City, USA. 15-17 September 1978.

For further information regarding this three-day course please contact Joshua A. Becker, MD, Department of Radiology, Box 1198, Downstate Medical Center, 450 Clarkson Avenue, Brooklyn, New York 11203, USA.

One-day Provincial Meeting: BAUS

Nottingham. 7 October 1978.

Further particulars from: Honorary Secretary, BAUS, Royal College of Surgeons, Lincoln's Inn Fields, London WC2.

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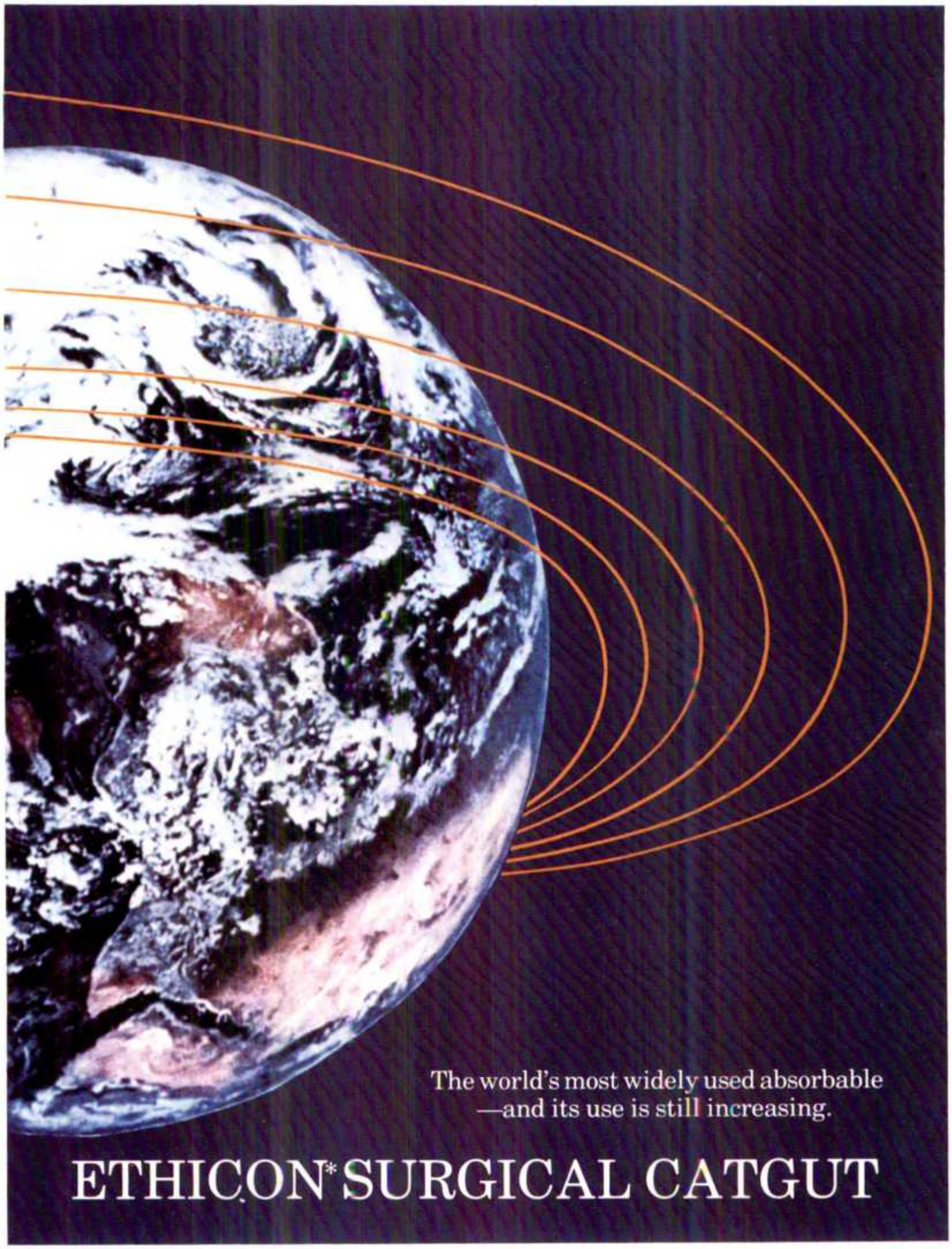
*Organisers wishing to have details of their courses and conferences published in the Journal should send details to J. E. Newsam, Western General Hospital, Edinburgh EH4 2XU.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348 Orchipexy in the Prune Belly Syndrome
John R. Woodard and Thomas S. Parrott

Case Reports

352 Antisperm Antibodies in a Case of Secondary Unilateral Testicular Atrophy
C. Laurenti, A. Fagioli, A. Lenzi and F. Dondero

353 Inversion of the Urinary Bladder
A. S. Thavarasah and L. S. Attygalle

354 Absent Dartos
Ahmed Shafik

355 Leukoplakia of the Penis—Bleomycin Treatment
R. Sakoda, M. Oka and K. Nakashima

356 Exstrophy-Variant of the Bladder
K. Kaye

357 Both Ureteric Orifices of the Same Side of the Bladder
A. M. K. Rickwood

358 Prostatic Adenocarcinoma with Ectopic ACTH Production
E. A. Molland

359 Book Reviews

360 Conferences and Courses

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British Journal of Urology

August 1978 Volume 50 Number 5

Original Articles

289 Radiograph Measurements and Contralateral Renal Size in Primary Pelvic Hydronephrosis
P. J. Milewski

294 The Relationship Between Urinary Bilharziasis and Urolithiasis in the Sudan
A. Ibrahim

298 Coagulum Pyelolithotomy
P. B. Smith, J. B. M. Roberts and M. Dunn

302 Calculi in Renal Transplants
B. St. C. Lucas and J. E. Castro

307 The Diagnosis and Treatment of Lymphocoeles Associated with Renal Transplantation. A report of 6 cases and a review of the literature
J. G. Brockis, J. C. Hulbert, A. S. Patel, D. Golinger, P. Hurst, B. Saker, E. F. Haywood, A. K. House and A. van Merwyk

313 Ureteric Involvement with Abdominal Aortic Aneurysm
J. L. Peters and A. G. A. Cowie

319 The influence of Early Post-Operative Intravenous Nutrition upon Recovery after Total Cystectomy
K. J. Foster, K. G. M. M. Alberti, N. Allen, J. Jenkins, A. MacIver, C. J. Smart and S. J. Karran

324 Polyglycolic Acid Versus Chromic Catgut in Bladder Surgery
O. Kronborg, A. Ostergaard, K. Steven and J. K. Gotrik

328 Adoptive Immunotherapy and Radiotherapy in the treatment of Urinary Bladder Cancer
M. O. Symes, H. Eckert, R. C. L. Feneley, Teresa Lai, J. P. Mitchell, J. B. M. Roberts and C. R. Tribe

332 Alpha-Adrenergic Agents in Urinary Disorders of the Proximal Urethra
Part I. Sphincteric Incontinence
S. A. Awad, J. W. Downie and H. G. Kiruluta

336 Alpha-Adrenergic Agents in Urinary Disorders of the Proximal Urethra
Part II. Urethral Obstruction due to "Sympathetic Dyssynergia"
S. A. Awad, J. W. Downie and H. G. Kiruluta

340 Congenital Parameatal Urethral Cyst in the Male
M. Oka, K. Nakashima and R. Sakoda

342 Recanalisation of Vas after Vasectomy. Evaluation of Various Techniques in Dogs
O. P. Taneja, N. K. Tagore, V. Tagore and S. M. Gulati

Continued on Inside Back Cover]

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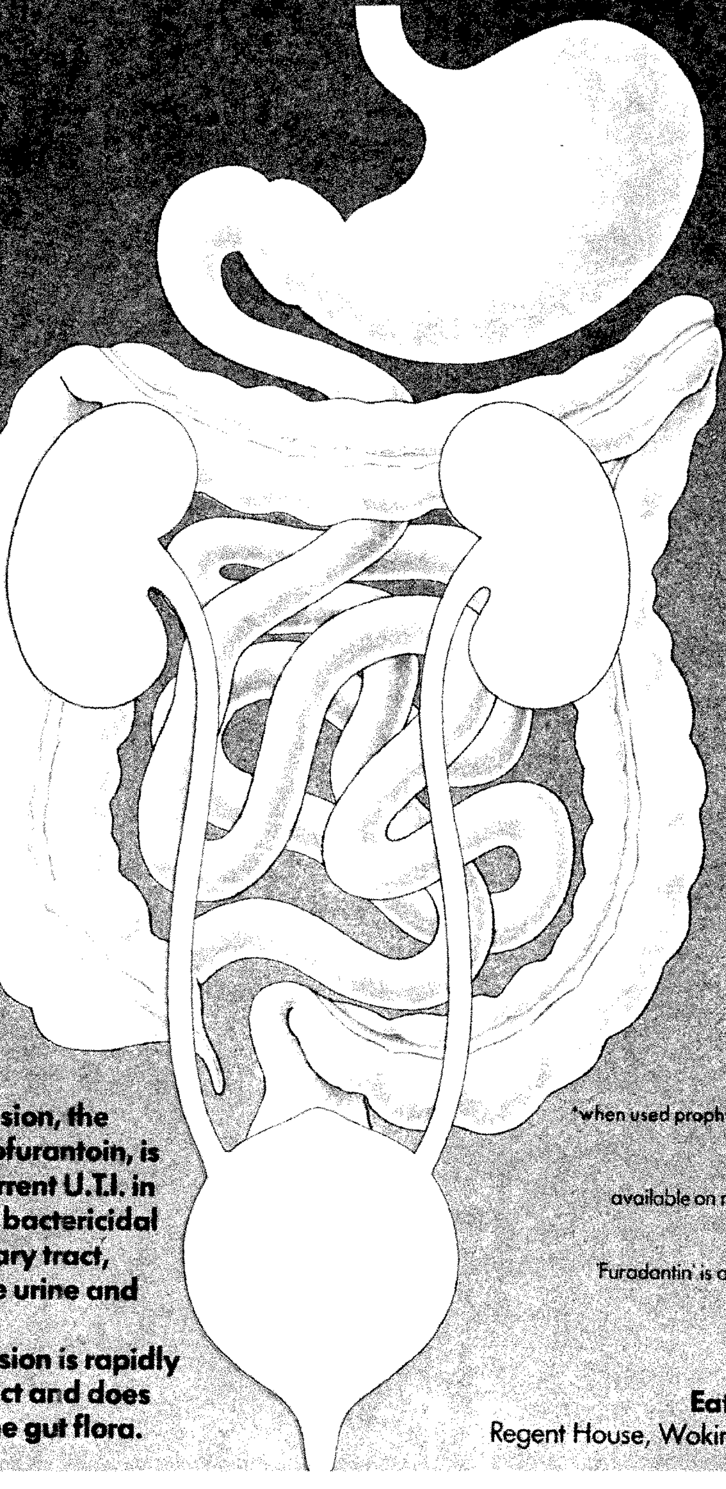

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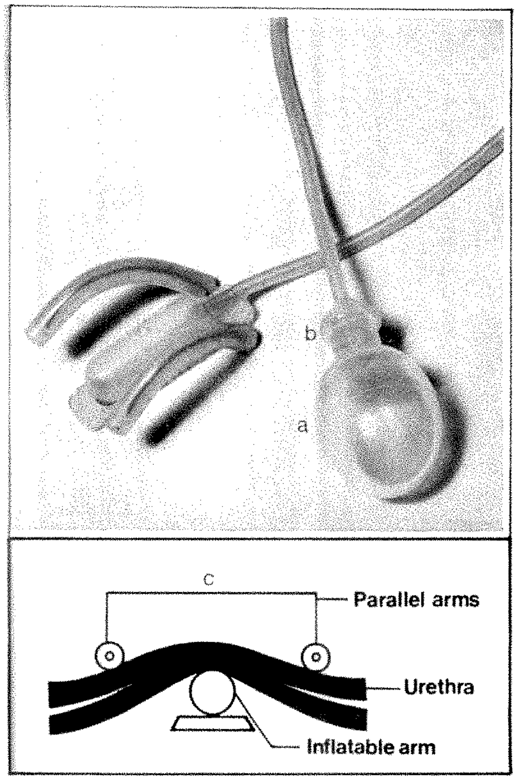

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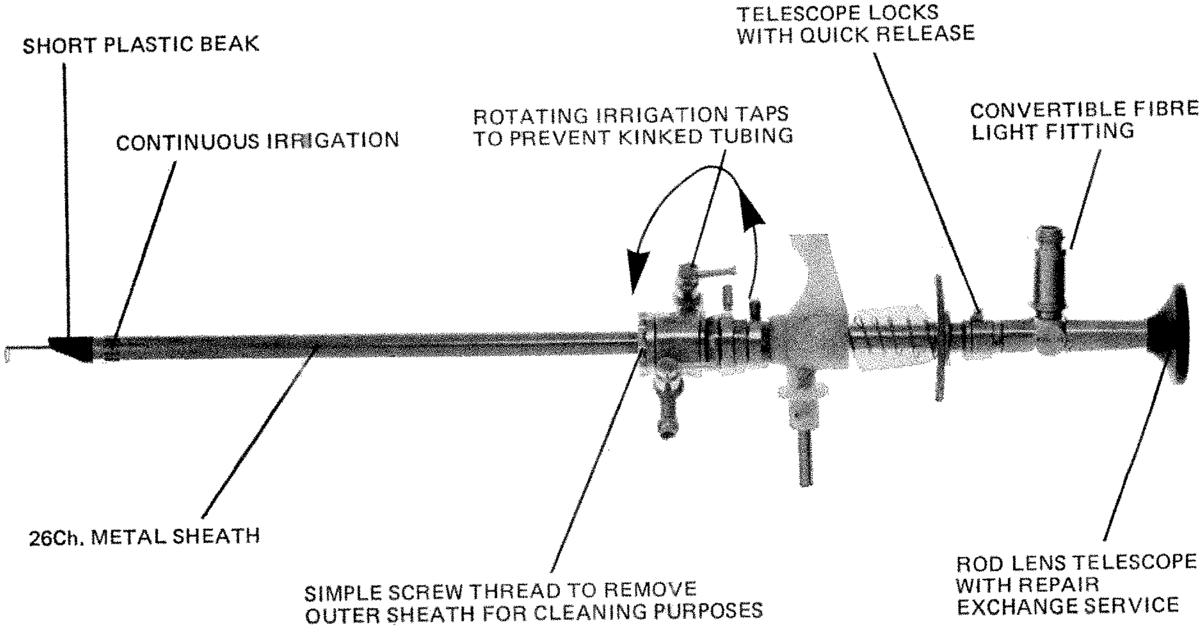
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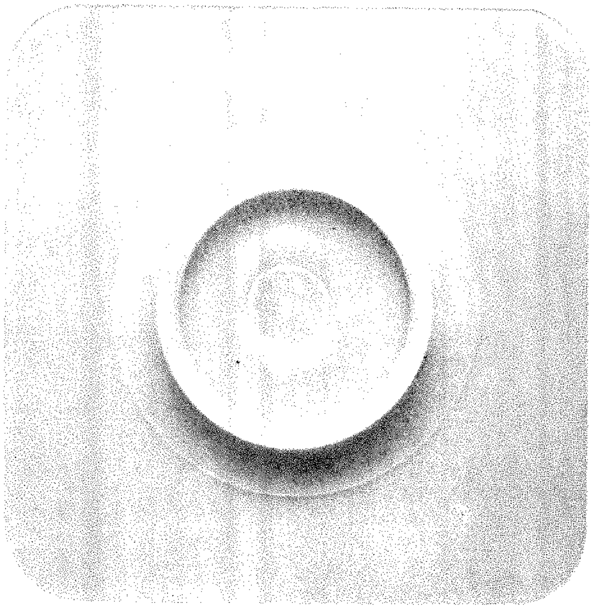

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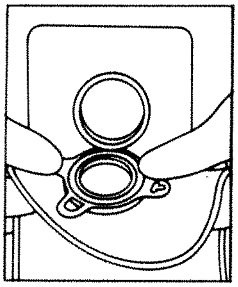

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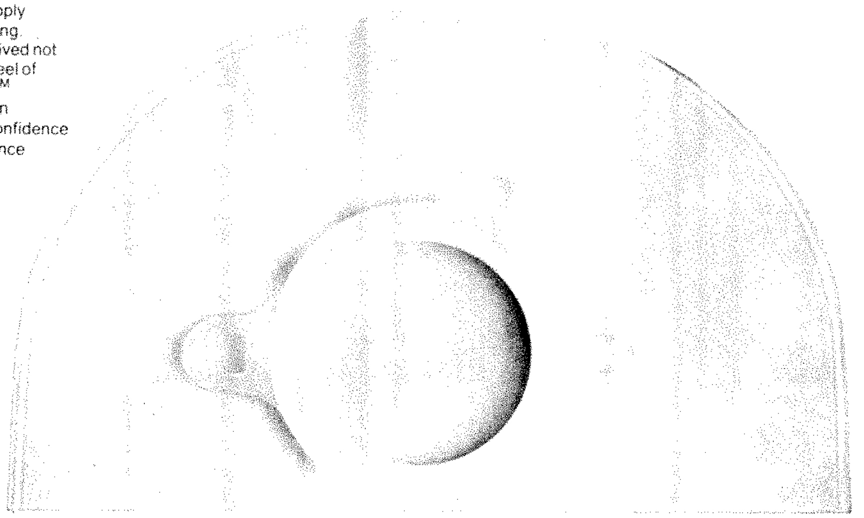

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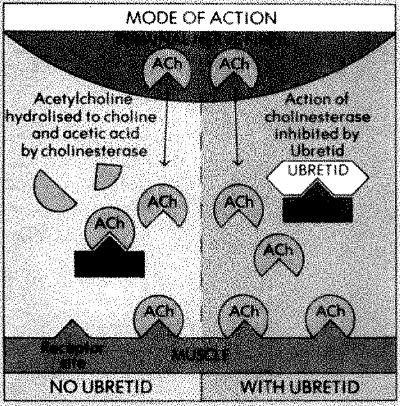
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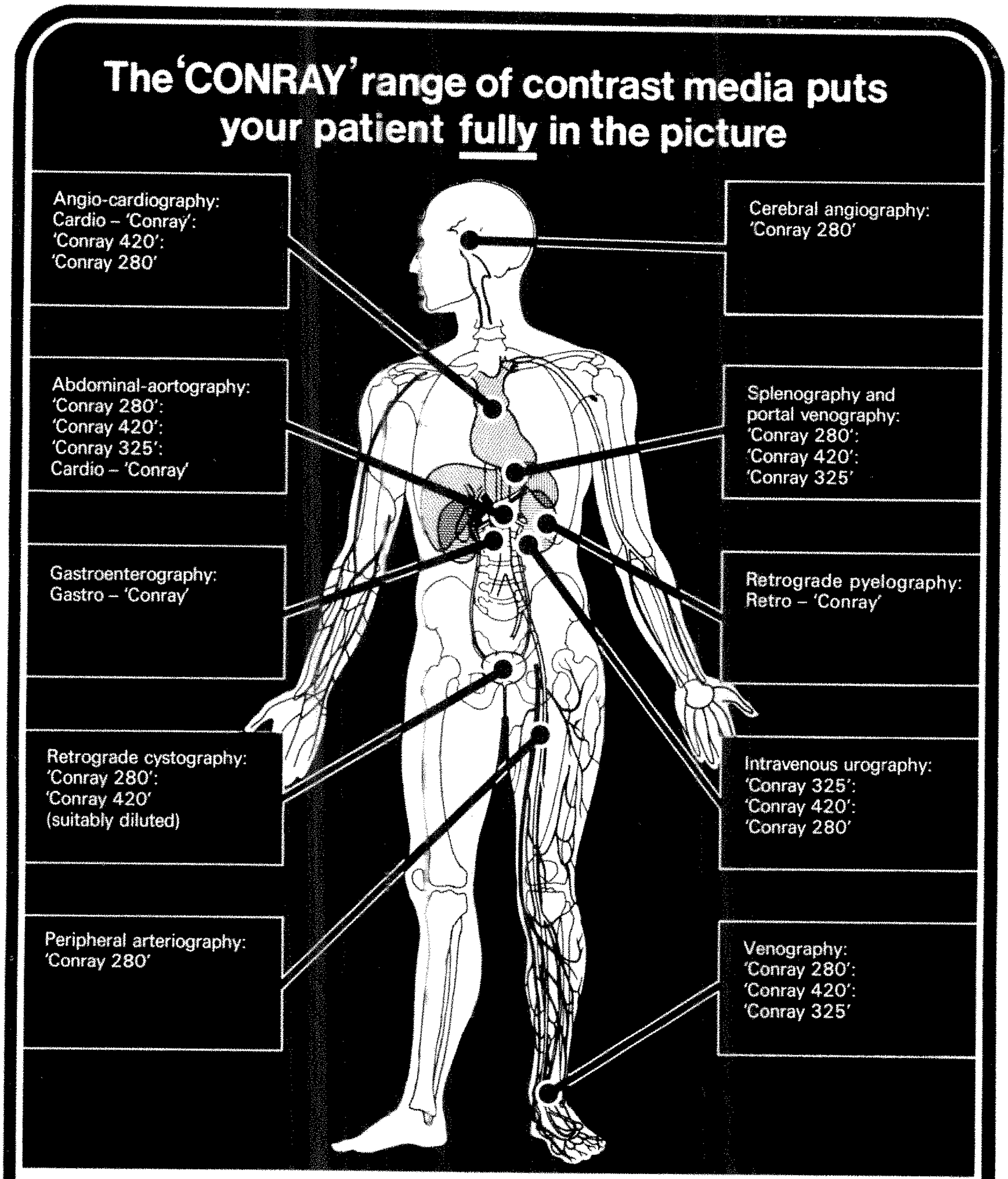
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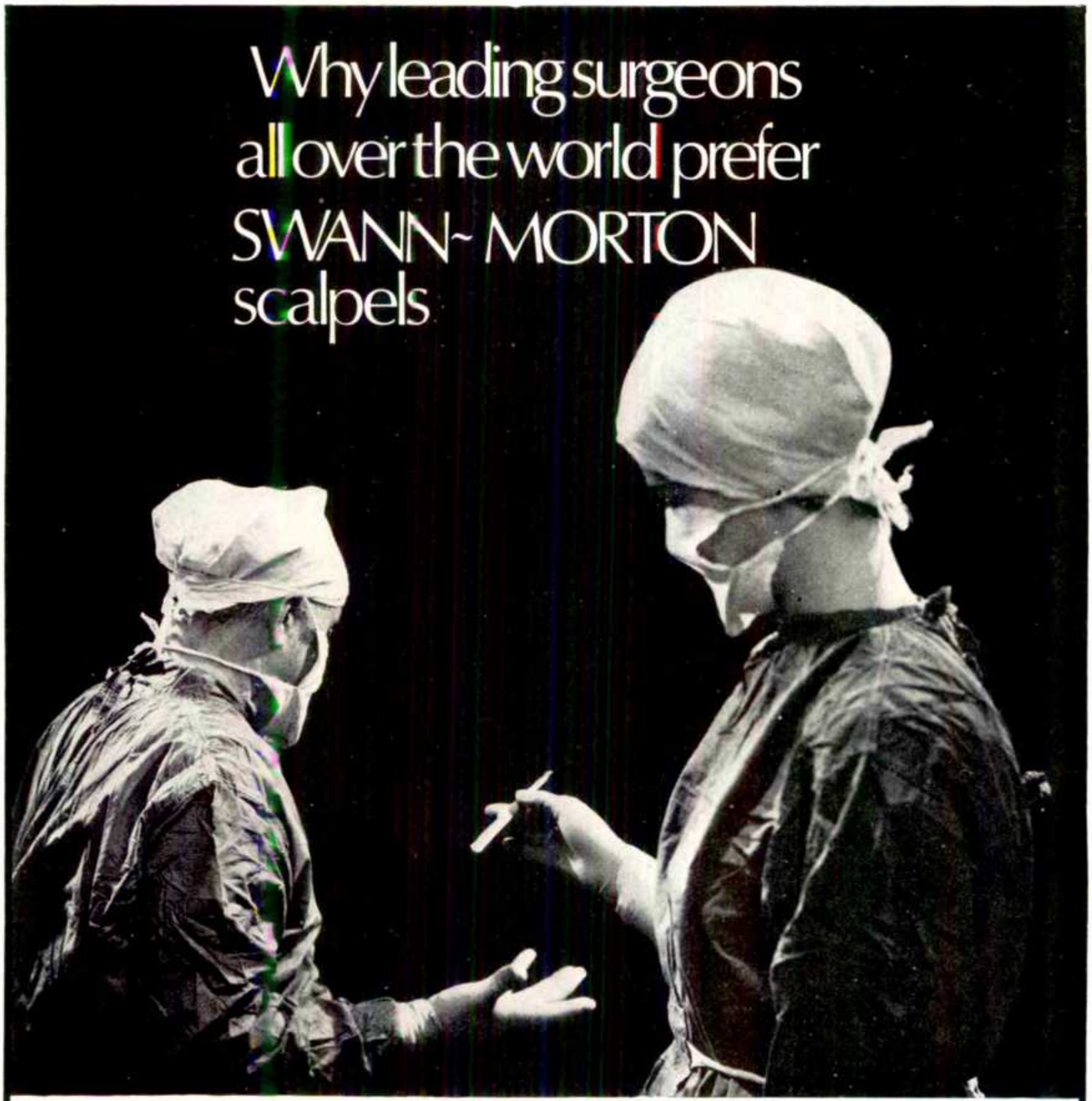
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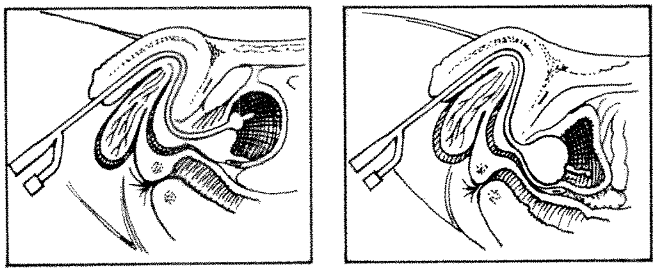

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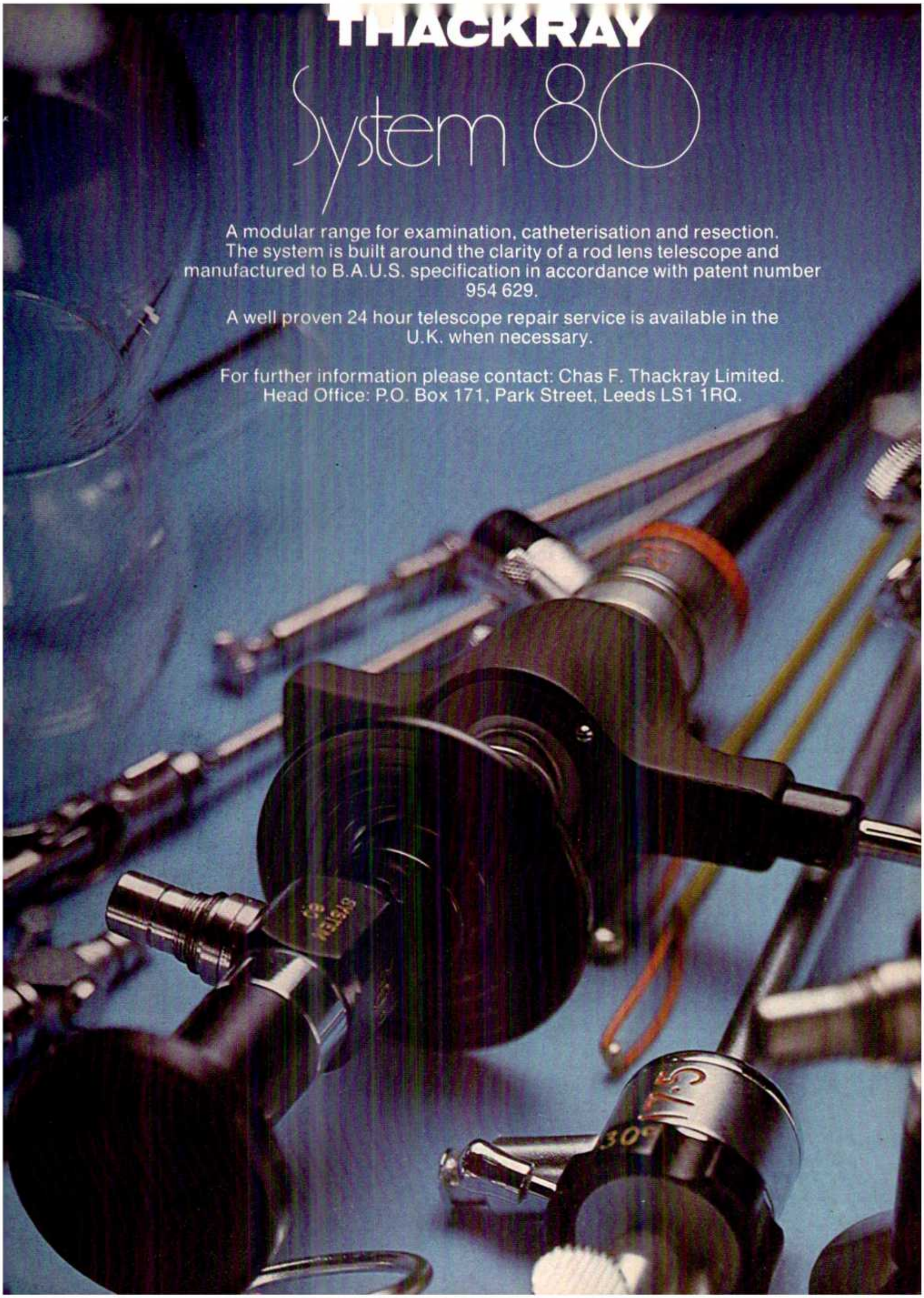

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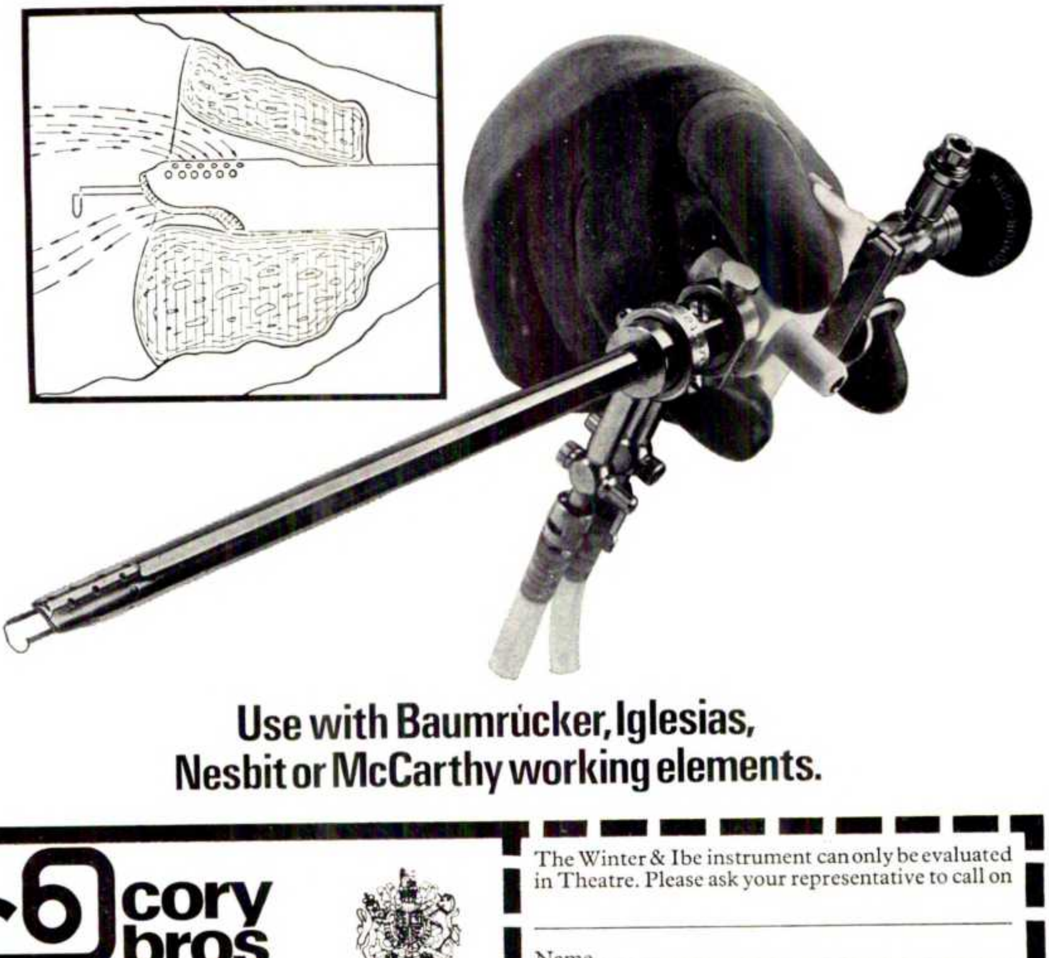

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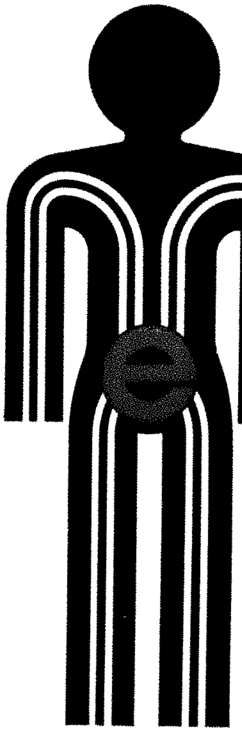

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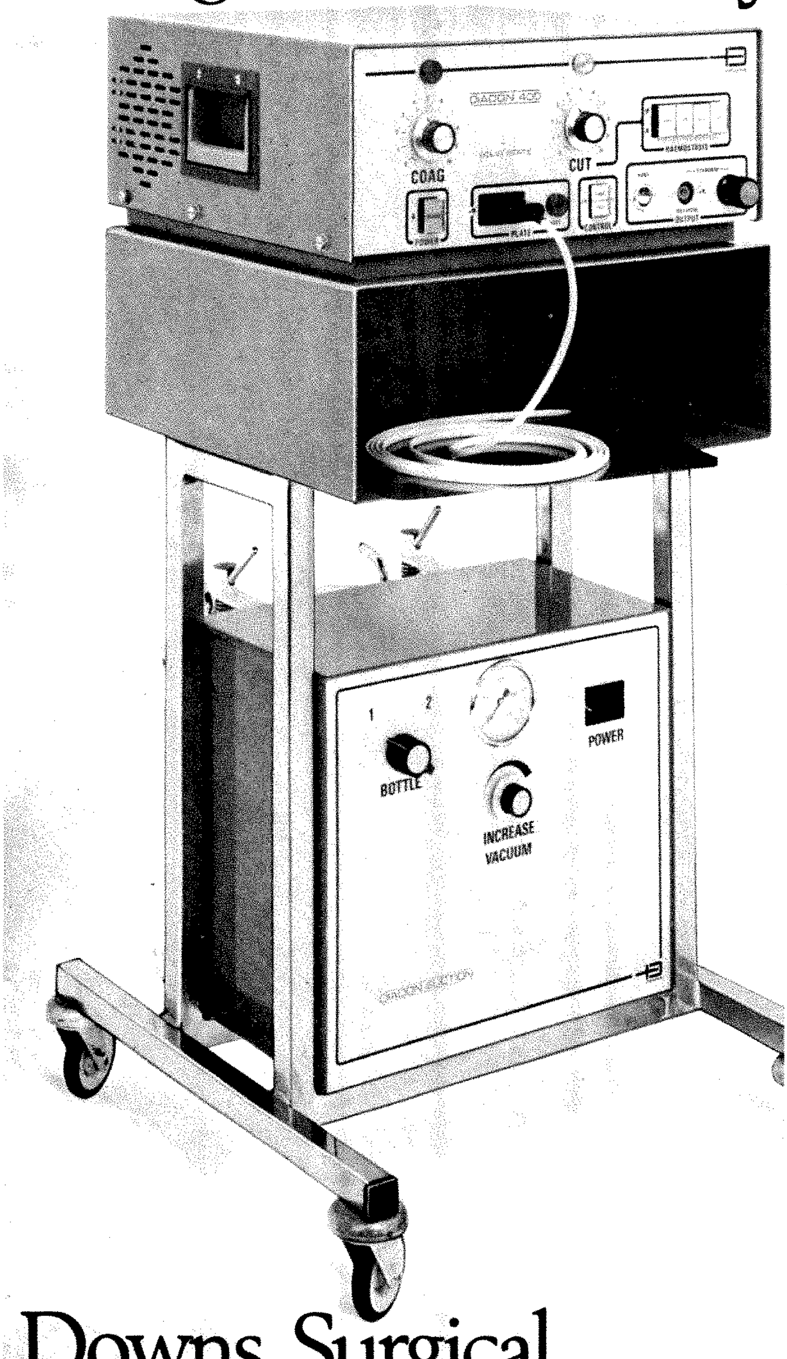

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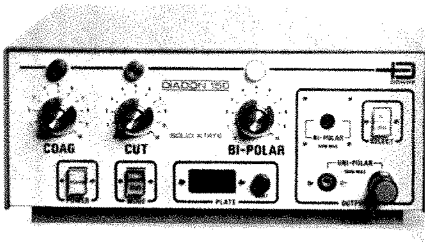

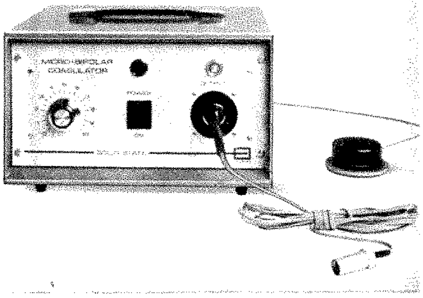

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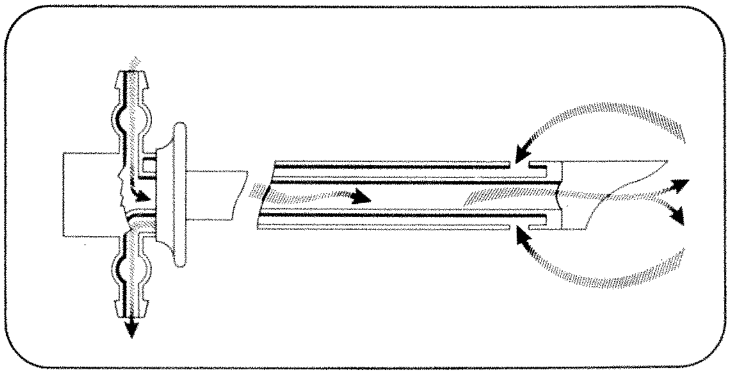

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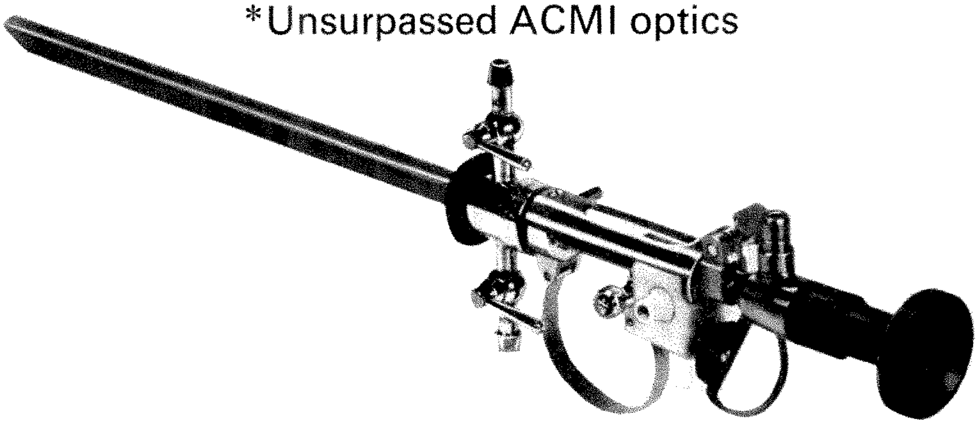

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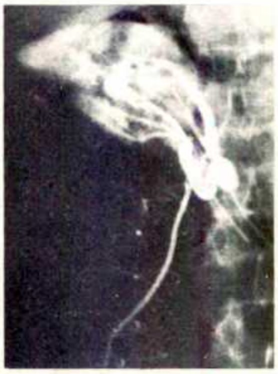

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REF: Woodside, J.; Schwarz, H.; Bergreen, P.: Peripheral Embolization Complicating Bilateral Renal Infarction With Gelfoam. American Journal of Roentgenology: Vol. 126: 1033-1034, 1976.

Gang, D.L.; Dole, K.R.; Adelman, L.S.: Spinal Cord Infarction Following Therapeutic Renal Artery Embolization. JAMA: VOL. 237, No. 26, June, 1977.

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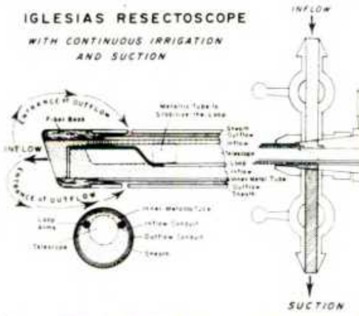

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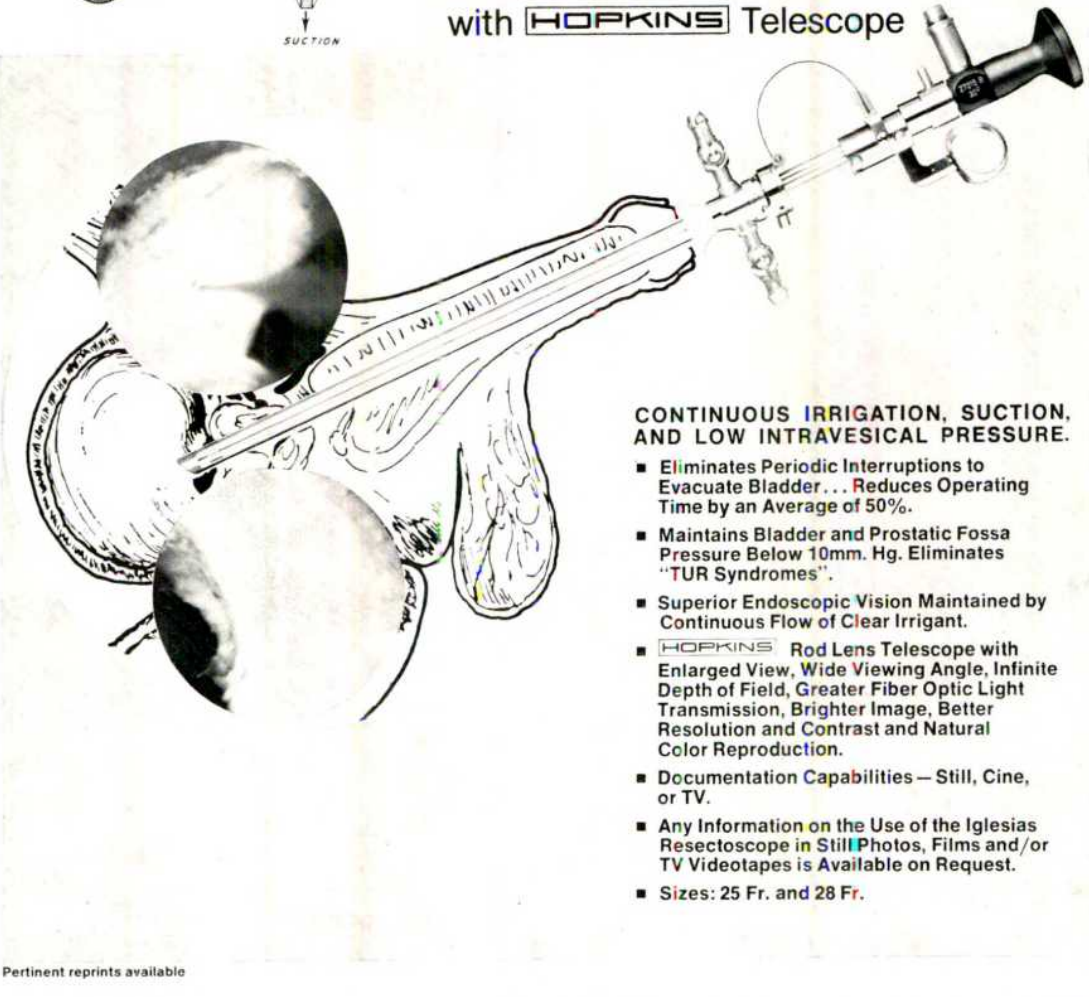

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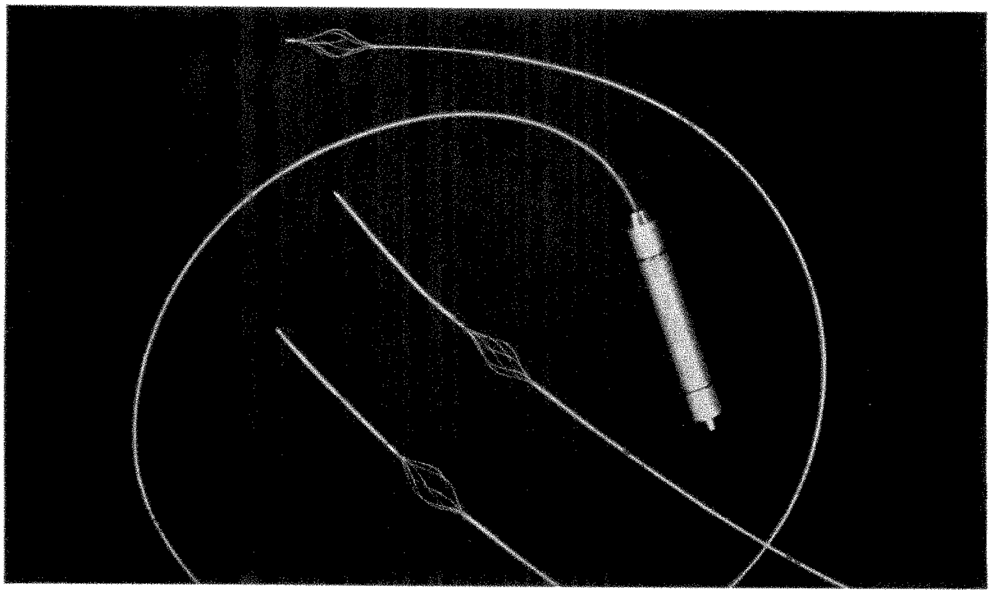

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British Journal of Urology (1978), **50**, 361-366

Report of the Standing Committee on Urological Instruments: Endoscopes

J. P. MITCHELL, J. BLANDY, J. G. GOW, C. H. KINDER, R. T. TURNER-WARWICK and J. F. R. WITHYCOMBE

Some 5 years ago Mr David Wallace, then President of the Section of Urology of the Royal Society of Medicine, wrote to the Council of BAUS expressing concern that British manufacturers of endoscopic instruments were falling behind in the development of urological endoscopes. He pointed out that the solid rod lens system, designed and developed by Professor Harold Hopkins of Reading University, had ultimately been taken up by an overseas manufacturer, and the patent rights had subsequently excluded manufacturers of all other countries, despite the fact that it was a British invention. He questioned whether there was adequate liaison between urologists using endoscopic equipment, and the manufacturers. He pointed out that prices for new equipment and for repairs had increased phenomenally and that the time taken to repair equipment was variable and unpredictable. Your Council accepted this letter and appointed a Committee (Table 1) to look into these problems and to report back to the Council.

Table 1

J. P. Mitchell, Bristol—Chairman

J. G. Gow, Liverpool
R. T. Turner-Warwick, Middlesex Hospital, London
D. M. Wallace, The Royal Marsden Hospital, London
J. F. R. Withycombe, Cambridge

In the first instance, the Committee concentrated on investigating the patent rights and carrying out a survey on the repair service available from all manufacturers. The means by which the rights of the solid rod lens system left the United Kingdom, having originally been owned by Watsons, was a long and involved story which took our Committee many months to unravel. Part of its transit was via a firm which constructed long range optical gun sights and had its chief interests based in Holland. Whether as a result of the enquiries from our Committee or whether it was due to the impending time expiry of the rights, it is of interest to report that within 12 months of this Committee's starting work, all manufacturers of endoscopes, both in Europe and in America, had openly stated their intention of constructing solid rod lens telescopes as soon as they could develop the essential know-how in optical physics. One British firm purchased the right to manufacture solid rod lens telescopes and to market these within certain geographical limitations.

The findings of these investigations into the rights, and the survey of repair facilities available in this country were reported back to Council 2 years ago. It was following this that the Council of BAUS set up a Standing Committee for Urological Instruments, with broad terms of reference, to consider and, if possible, assess the quality, durability and versatility of various instruments in frequent use by urologists. The additional members invited to join the Committee are listed in Table 2, including our 2 worthy secretaries in succession. The first and obvious choice was endoscopic instruments. With the impecunious state of our National Health Service, the market cost of these instruments was to be an important factor in our considerations. It was surprising that, despite the economy value of such an investigation, remarkably little interest could be aroused in the portals of the Elephant and Castle, Euston Towers and Russell Square. It says much for the loyalty of our profession that BAUS should have persisted with this investigation,

Table 2

J. P. Blandy, The London Hospital
C. H. Kinder, Guy's Hospital, London
J. P. Williams, Institute of Urology, London
E. Charlton Edwards, Manchester

Read at the 33rd Annual Meeting on the British Association of Urological Surgeons in Aberdeen, June 1977.

despite the lack of support from the Department of Health and Social Security who were to be, in fact, the principal beneficiaries of the financial economies which were bound to come from such an investigation. The tentative offer made by the DHSS to purchase one set of each manufacturer's equipment only resulted in a delay in this investigation, while the DHSS left the project in their "pending" file for 9 months and still failed to give us any positive answer.

Ultimately, after discussion with all the manufacturers, they themselves made the very welcome suggestion that they would bring their instruments to each member of the Committee in turn for testing in use and would also submit their instruments to tests by an independent physicist. The manufacturers who agreed to submit their instruments to this testing are shown in Table 3. One other manufacturer, Winter and Ibe of Germany, was also approached but declined to partake in the investigation. The aim was both to assist urological surgeons in their selection and choice of equipment and to give constructive criticism where it was felt that it could be helpful to the manufacturer. It was hoped that the investigation would promote the liaison between user and manufacturer and, in this respect, the function of this Committee has been 100% successful. The Committee would like to express their gratitude to all the manufacturers and their agents for the extremely helpful and courteous co-operation in this time-consuming exercise, as all the manufacturers took their instruments to each of the 6 centres carrying out the test, each visit lasting 2 days, as well as to Mr A. T. Makepeace of Bristol University, who supervised the optical measurements and calibration of the instruments. In view of this support given by the manufacturers, the Committee felt that all criticism should be constructive.

As well as the physicists' optical assessment, an extensive *pro forma* was circulated for each member of the Committee to report on each instrument. The results of these findings were collated and this report is a brief resumé of some of the major points of interest. The full report is available for perusal by BAUS members in the secretariat rooms of the Royal College of Surgeons of England.

Table 3 The Manufacturers Who Agreed to Submit Their Instruments for Testing

The American Cystoscope Manufacturers Inc. (Wappler Ltd)
The British Cystoscope Company (Thackrays Ltd)
The Endoscopic Instrument Company
The Genito-Urinary Manufacturing Company
Karl Storz K.G. (Rimmer Bros.)
Richard Wolf Endoscopes (Downs Surgical Ltd)

Telescopes

It is appreciated that the investigation gives no indication of the durability of the instruments with use, as these were new telescopes. However, with the exception of ACMI, the equipment of all manufacturers was in regular use at one or other centre, and therefore a subjective assessment could be made only on the instruments that had been in use within that particular department. On the other hand, the lack of any identity number, such as earlier telescopes used to carry, made it impossible for any of us to record exactly how long each telescope had been in service when it had to go away for repair. Furthermore, to identify telescopes with a number would have led to complications with supplies officers and theatre superintendents, when certain firms introduced an exchange repair service, because the hospital books would show a different number replacing the instrument that went for repair.

Some manufacturers felt they need provide only a fore-oblique telescope and a right-angled telescope, but the users were unanimous that the advantages of a direct vision telescope (0°) for urethroscopy and the viewing of the interior of a diverticulum outweighed the disadvantages of a multiplicity of endoscopes.

Although those manufacturers not providing a direct vision telescope claimed that the fore-oblique gave sufficient view straight ahead, in fact the beak of the sheath was just out of view, which increased the risk of damaging the mucosa of the urethra while advancing the instrument under direct vision. It was for this reason that all users agreed that manufacturers should be encouraged to provide a 0° telescope in their range.

Those users who tested the Storz 120° (retrograde viewing telescope) were impressed by its usefulness in the circumstances when the anterior wall is acutely angled on the bladder neck or where there is a marked enlargement of the middle lobe of the prostate, which obscures the trigone when viewed with a right-angled telescope. Since starting this trial Wolf has now produced both a direct vision and a retrograde viewing telescope.

The wide field of view provided by the Storz telescope was considered by all users as a great advantage in the 70° telescope. On the other hand, the wide field of view was of dubious value in the direct vision telescope and a distinct disadvantage in the fore-oblique telescope, as it reduced the magnification of objects at a distance of 2 to 3 cm from the telescope and gave the illusion of excessive distance travelled by the resectoscope electrode. It also increased the risk of burning the end of the telescope, owing to the closer proximity of the loop to the objective window at the end of its traverse during a resection. This information was something of a relief to the manufacturers as they were all receiving burnt telescopes for repair, a problem which has now been overcome by tightening up the tolerances of the loop traverse so that it does not overlap the telescope, secondly, by improving the stabilisers on the loop electrode and, thirdly, in the case of the Storz telescopes, by the reduction in the wide angle on their fore-oblique.

It was surprising that the additional length of the Storz adult telescope passed with little comment. Although no user stated that any of the other telescopes were of inadequate length, many of us at times will have been faced with circumstances under which we have found telescopes too short to reach the interior of the bladder.

All telescope systems were capable of viewing satisfactorily from a distance of 3 mm up to 5 cm. The need for close-up viewing without loss of focus is, of course, increased with the wide-angle lens which, in itself, reduces the magnification.

No adverse comments were made regarding eyestrain with any manufacturer's products. Eyestrain following long endoscopic procedures can be due to a variety of factors: firstly, the careful control of the intensity of illumination; secondly, the position of the image as viewed through the eyepiece, which seemed to be more comfortable when viewed at infinity; and thirdly, the size of the image subtended at the eye, which was larger by more than 25% in the Wolf Luminar System than in any of the other telescopes. In addition to the easing of any risk of eyestrain, this imaging at infinity makes photography more convenient, as there is no need for special calibration of each individual telescope. No adverse comment was made on the colour which, again, could be adjusted to some extent by the intensity of illumination. Some of the earlier Storz telescopes changed to a yellowish tinge over a period of 2 to 3 years, though the clarity of the telescope remained unaffected. This change of colour was presumably due to the cement between the rod lenses, but those users who have had new Storz telescopes within the last 3 years corroborate the claim by Storz that this problem appears to have been overcome.

One of the most difficult features to assess was clarity of view and flare. Checking the telescopes by viewing fine graticules at a set distance, little difference between the telescopes could be found. At the same time, the users could not help commenting that the Storz telescope gave the clearest view. This was partly due to the intensity of light transmitted back to the eye via the optical system, and also partly due to reduction of flare to a minimum. Flare is a difficult feature to define even for a physicist, as, in principle, it is due to 2 factors—highly contrasting light and reflected light. For example, if a telescope is held up to the window, flare will be seen at the sides of the window. Figure 1 shows the numerous features contributing to flare by reflection from lens surfaces, from a highly polished sheath or loop electrode, or even from floating particles in the fluid medium.

Paediatric telescopes were not tested for comparison, as only 3 of the manufacturers produced fibre illuminated instruments less than 9 Charriere in diameter. In any case, all users were agreed that both Storz and Wolf paediatric telescopes were of very high reliable quality for the size of the instruments.

The eyepieces of all telescopes have not been thoroughly tested. Certain manufacturers allowed the endoscope to be dismantled so that the eyepieces could be seen in detail and one of these has come under some criticism regarding the insulation. This is being carefully considered by both by the manufacturers and by the physicists and we hope to give a further report in due course. It should be stated that the spark transmitted through this particular eyepiece was of an intensity equal to that which is thought to exist under normal working conditions. The manufacturer concerned has immediately modified the construction of the eyepiece to meet the requirements specified.

Since starting this survey, the manufacturers have all reached agreement on a standard size and shape of eyepiece, which should readily accept any camera adaptor for photography.

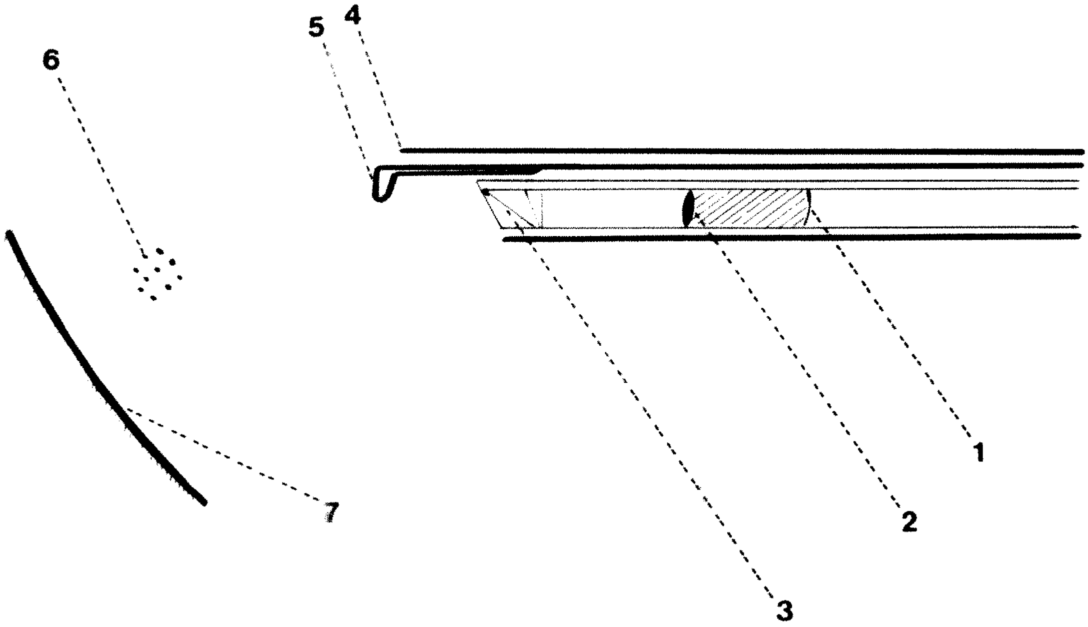

Fig. 1 Possible causes of flare: (1) Reflection on lens surface. (2) Reflection on lens interface. (3) Reflection on prism surface and window. (4) Reflection on tip of sheath. (5) Reflection on polished loop electrode. (6) Diffusion on particulate matter in the urine. (7) Excessive illumination of object being viewed.

Attempts were made to record the quality of each telescope by endoscopic photography. However, it very quickly became apparent that so much depended on the quality of the photographic equipment, the skill of the photographer and the selection of a photogenic view down the endoscope, that it was difficult to give any true comparison.

Cystoscope Sheaths

In addition to telescopes, the Committee also investigated the cystoscope sheaths and the other equipment provided as a standard set by the manufacturers. The quality of engineering was excellent in most cases. Storz equipment came out with the most favourable assessment. The equipment supplied by ACMI was regarded as excellent, though the range provided for testing was rather limited. Wolf had the most stable resectoscope electrode and, following the comments of this Committee, Storz have fitted a second stabiliser on their loops. Thackrays' equipment, excluding the telescopes, seemed to lack engineering finish, accuracy of tolerances and had evidently, in some instances, been sent out from the works without adequate checking.

Locking devices on endoscopes came in for universal criticism. There are 2 locks on every endoscope: the lock for the telescope and the lock for the bridging device into the sheath, or for the resectoscope moving parts into the resectoscope sheath. If the water pillar was fixed, then the location of the locking lever could readily be checked. However, as soon as the equipment was provided with a rotatable water collar (unanimously agreed by your Committee as an essential feature), it was found that in most instances there was no means of checking the accurate centring of the lock. It was felt that it would be a great advantage if both the lock for the telescope and the lock for the bridging device could be of a similar pattern. A new lock has received approval, designed by GU as a modification of a stud release lock originated by Endoscopic Ltd. At present GU fit this lock only on the telescope, whereas it is felt by the Committee that a similar lock for the bridging device, or the moving part of the sheath, should be considered.

Sterilisation or Disinfection of Endoscopes (Including Telescopes)

Wolf claimed that their instruments could be sterilised by all processes, including high pressure

Table 4 Price of Telescopes

	April 1976 (£)	*January 1977 (£)*	*August 1977 (£)*	*August 1978 (£)*
ACMI (Wappler Ltd)	585	585	585	597
Wolf (Downs Surgical Ltd)	481	550	593-630	609
Storz (Rimmer Bros.)	455	540-568	540-568*	567-596
Brit. Cysto. Co. (Thackrays Ltd)	380	380	437	480
GU Manufacturing Co. Ltd	-	-	375-385	424

All figures are exclusive of VAT.
* Subject to adjustment with Deutschmark to Sterling exchange.

autoclave—that is 134°C at 34 lb per sq in. In point of fact, however, none of the users put these instruments through such a high pressure autoclave procedure. All the other manufacturers were perefectly happy to accept low pressure steam up to 73°, gluteraldehyde or ethylene oxide up to 55°.

Repair Service

The repair service check, carried out about 2 years ago, left much to be desired and, in this respect, Thackrays provided the quickest service on an exchange basis. Both Wolf and Storz were found to have considerable delay as any major damage to equipment necessitated sending the instrument back to Germany. This, however, has been improved considerably, but the delay on major repairs can be anything up to 4 weeks for Wolf and 6 weeks for Storz, though with a good loan service from Rimmers. ACMI have, for several years, provided a loan service while the faulty telescope is away for repair. A loan service is now also available from Downs for standard Wolf equipment.

Any member of BAUS who is having considerable delay in the repair of equipment is advised to contact this Committee but, before writing in, you are advised to check carefully on your own hospital supplies department. The major delay discovered in this investigation was at the hospital supply level, where telescopes could take anything from 1 to 6 weeks from the operating theatre to the manufacturers via the supplies department, with a similar delay when the instrument returned after repair.

Cost

The fluctuating prices of these telescopes will be seen in Table 4, as quoted from various manufacturers at April 1976, January 1977, August 1977 and August 1978*.

In mitigation of Wolf's higher prices, it should be noted that modifications are readily considered by this firm, while Storz offer their equipment only as a standard range. For example, the cumbersome fibre-light pillar, which can obstruct lateral movement of the telescope, can be modified by Wolf and Thackrays at little extra cost.

Comment

The Genito-Urinary Manufacturing Company have very recently produced a solid rod lens telescope, which has not yet been through the tests of assessment by this Committee. Therefore the lack of favourable comment on the GU telescope is due to the fact that it was not available for assessment at the time these tests were carried out. Preliminary tests on the GU telescopes and accessories are promising.

In addition to testing endoscopes, your Committee has started work on a survey of the new solid state transistorised diathermy sets, of which several varieties have appeared on the market in the last 2 or 3 years. A report will be prepared indicating the actual advantage of these sets, the features to consider when purchasing, and a comparison of their safety standards.

Your Committee is also investigating the supply of sterile distilled water, low pressure steam autoclaves, and drainage tubes of silicone.

This report is brief and has only touched on the various aspects of the work being covered by your Committee. If you require further detailed information on any of these topics, or if you have any other particular items of equipment which you feel this Committee should investigate, the problem should be submitted to BAUS for the consideration of Council, who will, if approved, instruct this Committee to proceed. For 3 years now this has been a Standing Committee and its work will therefore continue as an on-going "watch dog" over your urological equipment.

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* 1978 prices have been added since this Report was presented. Editor.

British Journal of Urology (1970), **50**, 367-370

Renal Growth Following Reimplantation of the Ureters for Reflux

J. D. ATWELL and M. R. VIJAY

The Wessex Regional Centre for Paediatric Surgery, The General Hospital, Southampton

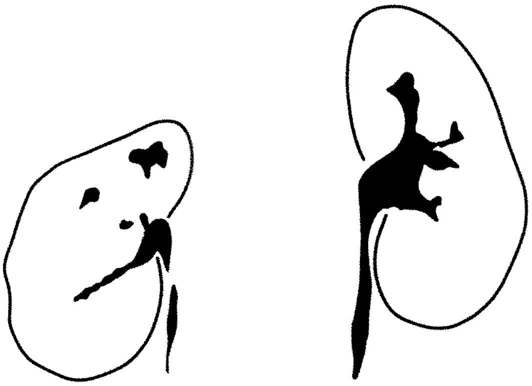
Summary—Renal growth after reimplantation of a refluxing ureter was measured in 17 patients (26 renal units). Measurements of renal length were made from intravenous pyelograms 1, 3 and 5 years post-operatively. Our findings showed that after successful antireflux surgery the rate of renal growth was greater than normal in the first post-operative year but between 1 and 5 years post-operatively was normal.

The primary aim of reimplantation of the ureter to cure vesico-ureteric reflux is to protect the kidney by preventing ascending infection and the development or the progression of renal scarring (Figs. 1a and b). One of the methods by which the effectiveness of the operation can be determined is by measuring kidney length as indicated from repeated pyelograms. These measurements can then be related to the age and height of the patient and thus allow an assessment of the normality or otherwise of renal growth (Hodson *et al.*, 1962). In a series of 17 patients who underwent either unilateral or bilateral reimplantation of the ureters in 1969 or 1970 we have assessed renal growth 1 year, 3 years and 5 years post-operatively and this article records our findings.

Patients and Methods

There were 4 males and 13 females. Bilateral reimplantation of the ureters was undertaken in 9 and unilateral reimplantation in 8 (3 right; 5 left). Thus a total of 26 renal units was studied. The age of patients at operation ranged from 2 years 8 months to 14 years 5 months. The length of post-operative follow-up was longer than 5 years in 11, between 3 and 5 years in 5, and 1 year in 1. The mean length of follow-up was 6.7 years.

The vesico-ureteric reflux was primary in 14 patients, secondary to a para-ureteric diverticulum in 2 and due to double ureters in 1. Reflux was present in 25 of the 26 renal units studied. Grade IV reflux existed in 10 patients, Grade III in 2, Grade II in 1, Grade I in 4; thus in 14 of the 17 patients the reflux was either Grade III or IV.



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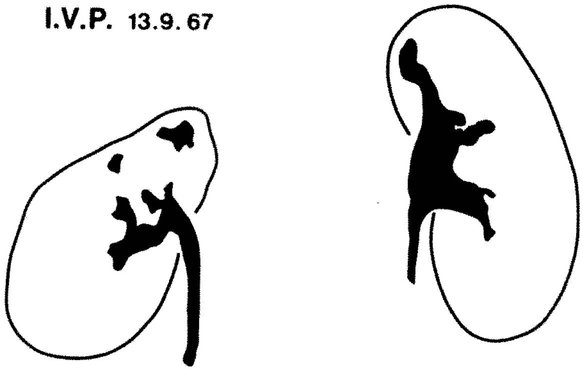

I.V.P. 20.2.70

Fig. 1a Patient 17. Bilateral vesico-ureteric reflux. Tracings of IVPs in 1967 and 1970 showing failure of growth of the right kidney and a new scar developing in the left kidney. Bilateral reimplantation of ureters 23.2.70.

Received 19 January 1978.
Accepted for publication 21 April 1978.

Results

Intravenous pyelograms were carried out pre-operatively and 1, 3 and 5 years post-operatively. Measurements of renal length were made from these radiographs and plotted against the age of the patient. In our series the heights of the patients were not always recorded in the early stages of the review and we have therefore used the age of the patient for our data. These measurements were used to compare the rate of renal growth following reimplantation of the ureters with the rate of normal renal growth (Hodson *et al.*, 1962). In normal children between 5 and 13 years of age the slope of the graph for age against kidney length is Y=0.379x+6.65 where Y is the length of the kidney in centimetres and X the height in inches (n=393, correlation coefficient 0.874).

Calculations of the mean renal length in our patients pre-operatively and 1, 3 and 5 years post-operatively had suggested that renal growth accelerated following successful reimplantation of the ureters (Fig. 2) and that this growth spurt was confined to the first post-operative year.

In view of these findings a comparison was made between the rate of growth between pre-operatively and 1 year post-operatively (n=52) and 1 to 5 years post-operatively (n=71). The rate of growth was initially Y=0.30x+6.82 (n=52, correlation coefficient 0.70) and between 1 to 5 years was Y=0.15x+8.63 (n=71, correlation coefficient 0.84). These results lie within 1 standard deviation of the rates calculated for normal renal growth (Fig. 3).

In 8 patients with unilateral reflux it was possible to compare renal growth following reimplantation with the growth of the contralateral normal kidney. In the reimplanted group Y=0.28x+7.20 (n=30, correlation coefficient 0.75) compared to Y=0.31x+7.16 (n=29, correlation coefficient 0.82) in the contralateral normal kidney. Thus the rates of growth were the same (Fig. 4).

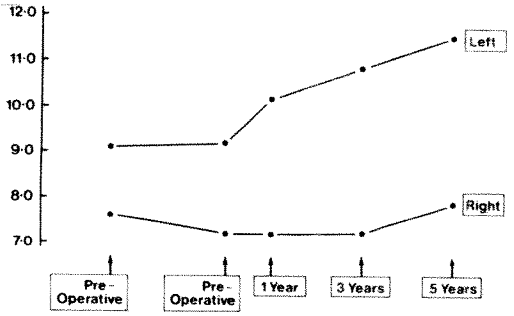

Fig. 1b Rate of renal growth in the same patient (17) before and after bilateral reimplantation of the ureters.

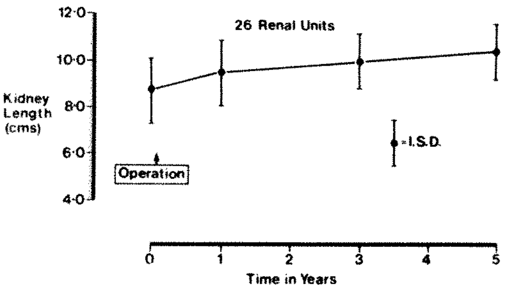

Fig. 2 Mean renal growth after reimplantation of the ureter 1, 3 and 5 years post-operatively.

In our observations, despite the small numbers in the series, the correlation coefficients found were remarkably similar to the reported correlation coefficient for normal renal growth (Table 1).

In 3 patients with bilateral reflux there was unilateral renal scarring. The rates of growth of these unilateral scarred kidneys were then compared to the rates of growth of the unscarred kidney following bilateral reimplantation of the ureters (Fig. 5). Thus scarring does not necessarily prevent renal growth, although there may be a latent period before the rate of renal growth returns to normal (Fig. 1b).

Discussion

Normal renal growth in children has been extensively studied. Hodson *et al.* (1962) found correlations between kidney size and the height and age

Table 1 Rates of Renal Growth*

		n	*Correlation coefficient*
Normal (Hodson *et al.*, 1962)	y=0.379x+6.65	393	0.87
0-1 year post-operatively	y=0.30x+6.82	52	0.70
1-5 years post-operatively	y=0.15x+8.63	71	0.84
Unilateral reimplanted ureter	y=0.28x+7.20	30	0.75
Contralateral normal ureter	y=0.31x+7.16	29	0.82

* y=length of kidney in centimetres. x=patient's height in inches.

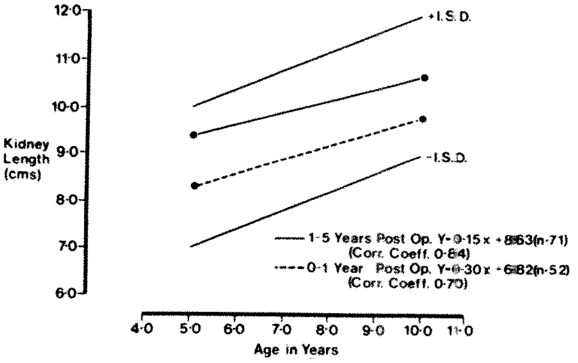

Fig. 3 Rate of renal growth after reimplantation of the ureters in the first year post-operatively compared to the rate of renal growth between 1 and 5 years post-operatively.

of the child and, provided accurate measurements of renal length are possible from standardised intravenous pyelograms, it is therefore possible to follow and record changes in the growth of the kidney. These authors based their observations on 393 patients using the mean of the combined length of both kidneys. In our series the length of each individual kidney was recorded. This may account for slight differences, especially as our sample was small compared with that of Hodson *et al.* (1962); despite this the observations on renal growth were well within 1 standard deviation of the normal. Of importance was the finding that renal growth in the unilateral reimplanted renal unit was very similar to the contralateral, non-refluxing kidney.

There have been few references to the rate of renal growth following reimplantation of the ureters. McCrae *et al.* (1974) noted that in ureters with gross reflux correction of the reflux was associated with the resumption of normal renal growth, while with lesser degrees of reflux there was no interference with renal growth; thus the severity of the initial reflux must be important when assessing renal growth. Willscher *et al.* (1976), in a review of 223 children who underwent antireflux surgery, found a statistically significant increase in renal growth, a finding confirmed in our series which showed a rapid rate of renal growth in the first 12 months following reimplantation of the ureters, after which renal growth continued at a normal rate.

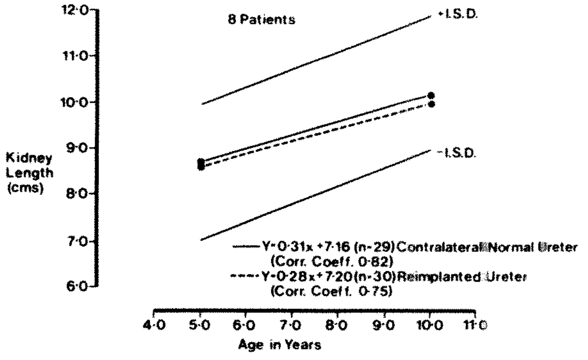

Fig. 4 Renal growth following unilateral reimplantation of a ureter. Note the similar rates of renal growth in both the reimplanted and the contralateral normal ureter.

Some evidence has been presented to suggest that a serum factor, renotropin, can stimulate damaged refluxing renal units to grow faster than normal after removal of the injuring stimulus (Lowenstein and Stern, 1963; Lytton *et al.*, 1969). Another explanation to account for alterations in renal growth before and after cure of reflux is based on alterations in renal tubular function. There can be no doubt that the water hammer effect of reflux has a deleterious effect on tubular function, whether associated or unassociated with infection. Radiological evidence of this is seen in the findings of intrarenal reflux in the experimental animal (Ransley and Risdon, 1974; Hodson *et al.*, 1975) and in the human with gross reflux.

Studies of tubular function have been recorded by Uehling (1971) who measured the concentrating ability of the kidney from a urine specimen obtained after an overnight fast in 44 normal children, in 46 children with urinary infection and a normal IVP and no reflux, and in 18 children with infection, reflux and a normal IVP. There was no significant difference in the concentrating ability with and without reflux and a

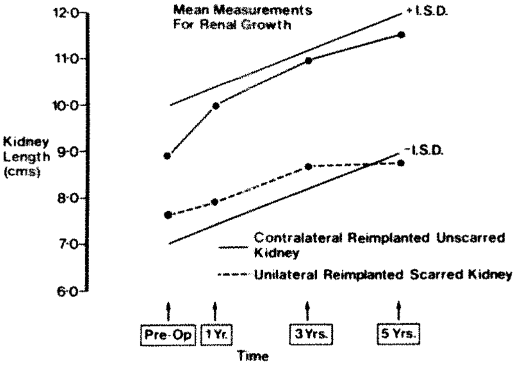

Fig. 5 Comparison of the mean rates of renal growth in patients 7, 14 and 17 with unilateral renal scarring preoperatively and following bilateral reimplantation of the ureters.

normal IVP. Despite this initial finding, a later article by the same author stated that there were changes in the concentrating ability after an antireflux operation (Uehling and Wear, 1976). In 27 children studied pre-operatively and 1 year post-operatively a mean increase in the maximal urinary osmolality of 80 osmoles per kg was found. In 15 of the 27 children there was increased concentrating ability 1 year post-operatively. In 3 children with post-operative ureteric obstruction the concentrating ability was lowered. Thus alterations in the concentrating ability of the kidney affect its growth and also the growth of the patient due to the correlation between renal length and the patient's height.

The results of our survey suggest that successful antireflux surgery results in accelerated renal growth in the first year post-operatively followed by a longer period of normal renal growth.

Acknowledgement

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An Evaluation of Techniques Used for the Production of Temporary Renal Ischaemia*

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Summary—Five techniques of producing temporary renal ischaemia have been evaluated in the rat. Damage was assessed by measuring inulin clearance, change in renal cortical intracellular water and ^{125}I-fibrin deposition.

Continuous renal artery occlusion produces significantly less renal damage than the other techniques commonly used.

Previous clinical and experimental investigations into the effect of varying periods of warm ischaemia on glomerulo-tubular function suggest that normothermic renal ischaemia should not exceed 30 min if permanent renal damage is to be avoided (Wickham *et al.*, 1967).

Post-ischaemic renal function has usually been assessed by either serial serum creatinine estimation or clearance tests. However, these parameters can be misleading because considerable renal damage can be demonstrated on renal biopsy despite apparently normal renal function (Rosenbaum *et al.*, 1967). For this reason it is doubtful whether conventional renal function tests accurately assess the severity of ischaemic damage caused by the various techniques presently used to produce warm renal ischaemia for the brief times used in clinical practice.

Cortical blood flow is not immediately re-established after transient renal ischaemia. This "no re-flow phenomenon" (Sheehan and Davies, 1959) is caused by swelling of the renal cortical cells and secondary microvascular coagulation (Ames *et al.*, 1968; Summers and Jamison, 1971). Cell swelling can be measured by changes in the renal cortical intracellular water (McLoughlin *et al.*, 1974) and renal microvascular coagulation by ^{125}I-fibrin deposition (Salaman, 1972).

The aim of this experimental study was to compare the effect of 30 min renal ischaemia produced by the 5 main methods that may be used in clinical practice: continuous clamping of the renal artery, intermittent clamping of the renal artery, continuous clamping of the renal pedicle, intermittent clamping of the renal pedicle and compression of the renal cortex. The results were assessed by measuring renal function with inulin clearance studies and by the "no re-flow phenomenon" as determined by changes in intracellular water and ^{125}I-fibrin deposition.

Material and Methods

A total of 245 adult Wistar rats (240-380 g) was used in these experiments. Each animal was anaesthetised with ether and both kidneys were mobilised through a midline incision using a "no-touch" technique; 0.1 ml of 1% procaine hydrochloride was injected around the renal vessels. Aortic blood pressure was monitored at the level of the renal arteries through a cannula inserted via the femoral artery using a blood pressure transducer and a Devices M19 recorder. Throughout the experiment the animal's body temperature was maintained by a heat lamp and the renal cortical temperature was monitored with a Thermistor probe. After 30 min of stable normotension with a renal cortical surface temperature of 37° ± 0.6°C, a 10 × 2 mm Schoville-Lewis artery clamp was applied to the renal artery or to the pedicle either continuously for 30 min, or intermittently by releasing it for 2 min at the end of each 10 min ischaemic period. Alternatively, an 0.5 cm incision was made at one pole of the

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kidney and haemorrhage prevented by gentle compression of the cortex with artery forceps for 30 min before suturing the incision.

The renal injury produced by each technique was assessed in 3 different ways, either daily up to 5 days after the initial experiment, or at 5-day intervals up to 20 days, after re-anaesthetising the animals.

Inulin Clearance Studies

The femoral vein and the ureter were cannulated. A solution of inulin in 3% Mannitol dissolved in isotopic saline was delivered into the vein at a constant rate of 0.2 ml per min by an infusion pump. After 1 h to allow for stabilisation of urine output, urine was collected at 10 min intervals. Blood samples were taken at the mid-point of each collection period. Inulin estimation in blood and urine was determined in the alkali-stable form using the method of Walser *et al.* (1955). Inulin clearance results are expressed in ml per min per 100 g rat weight. Thirty-five rats were used for these experiments, 10 in a control group and 5 in each ischaemic group.

Intracellular Water Estimation

Five rats from each ischaemic group were used at 5-day intervals up to 20 post-ischaemic days for renal cortical intracellular water estimation. A cortical biopsy of approximately 200 mg was taken, gently blotted and divided into 2. One piece was weighed wet and re-weighed after drying for 24 h in an oven at 106°C; the total tissue water was then derived. The remaining piece of cortical tissue was used for estimation of the extracellular (inulin) fluid space according to the method of Flear *et al.* (1960).

The intracellular water was calculated by the difference between the total tissue water and the extracellular (inulin) space, divided by the tissue dry weight and expressed as kg per kg dry solids of renal cortical tissue. One hundred and ten animals were used in these experiments, 10 in the control group and 20 in each ischaemic group.

^{125}I-Fibrin Deposition

The technique used and the preparation of rat ^{125}I-fibrinogen were as described by Salaman (1972). A solution of 10% rat ^{125}I-fibrinogen was injected into the internal jugular vein at the time of the original experiment before the production of renal ischaemia. In this group of rats only one kidney was made ischaemic. A total of 100 animals was used. At 5-day intervals of up to 20 post-ischaemic days bilateral nephrectomy was performed on 5 rats from each ischaemic group. After flushing with Hartman's solution the kidneys were weighed and then placed in a well-type scintillation counter. The radioactive count results were expressed as the radioactivity index, which is the ratio of counts per gram of ischaemic kidney to counts per gram of non-ischaemic kidney.

In all experiments the mean and standard error

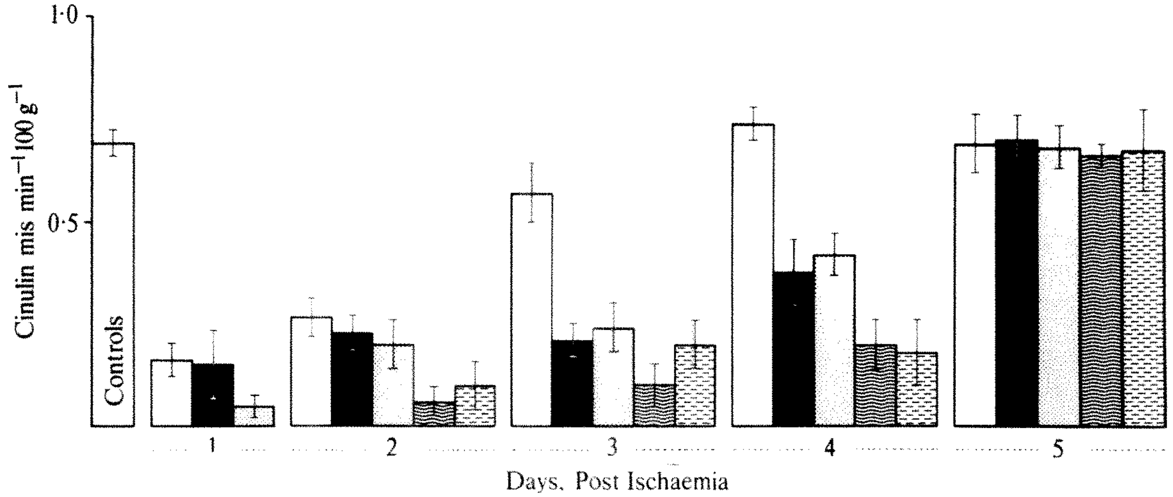

Fig. 1 Inulin clearance ($\bar{x} \pm 2$ SEM) following 30 min renal ischaemia produced by: continuous clamping of the artery ▭ or pedicle ▬; intermittent clamping of the artery ▭ or pedicle ▤; or manual compression of the renal cortex ▨.

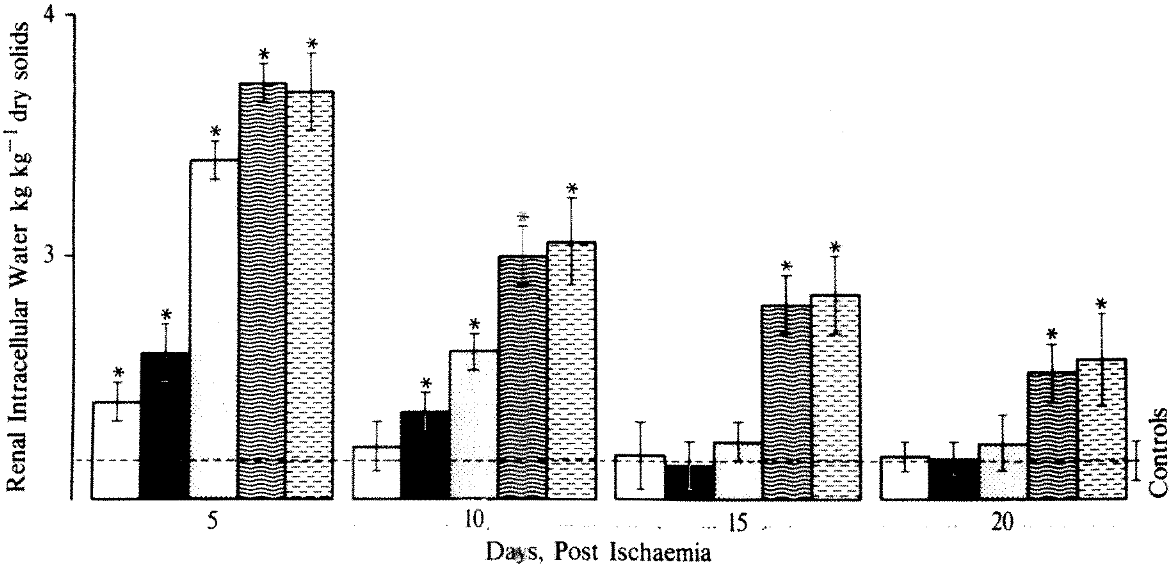

Fig. 2 Renal intracellular water ($\bar{x} \pm 2$ SEM) following 30 min renal ischaemia produced by: continuous clamping of the artery ☐ or pedicle ■ ; intermittent clamping of the artery ☐ or pedicle ▤ ; or manual compression of the renal cortex ▤ . *$P<0.001$.

of the mean of the results in each experimental group was calculated and compared using Student's t test. A P value at the 5% level or less was accepted as significant.

Results

For 48 h post-ischaemia, inulin clearance was significantly reduced irrespective of the technique used for its production (Fig. 1). By 72 h inulin clearance did not differ significantly between control animals and those in which continuous renal artery clamping was the method used for producing ischaemia. In all other groups inulin clearance remained significantly reduced compared

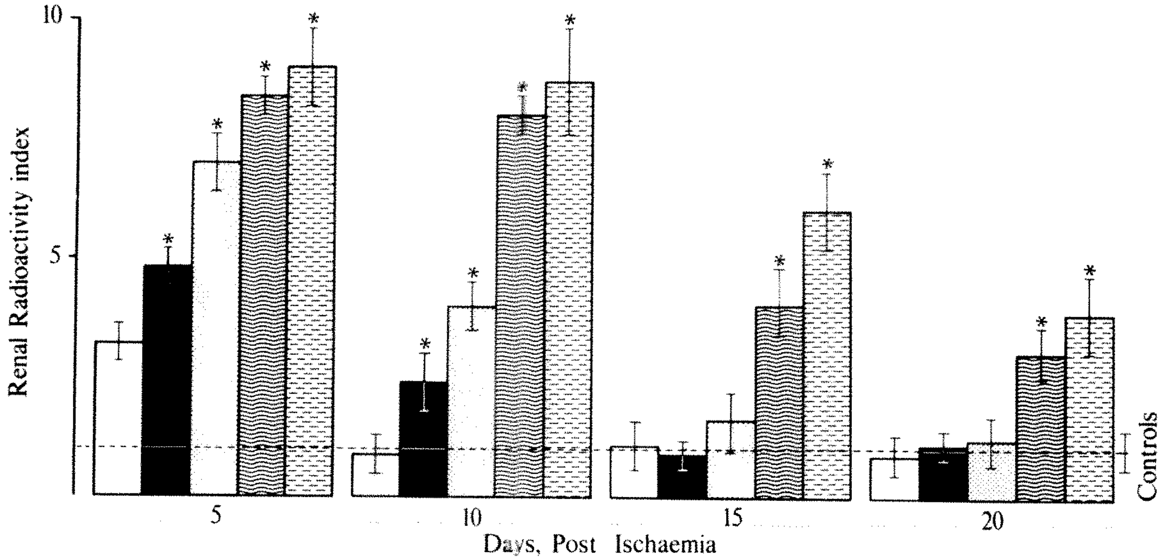

Fig. 3 Renal ^{125}I-fibrin deposition following 30 min renal ischaemia produced by: continuous clamping of the artery ☐ or pedicle ■ ; intermittent clamping of the artery ☐ or pedicle ▤ ; or manual compression of the renal cortex ▤ . ($\bar{x} \pm 2$ SEM) *$P<0.001$.

Table 1 Consultant Surgeons' Preferences for Production of Renal Ischaemia

No. of surgeons	*Max. tolerated period of normothermic ischaemia (min)*	*"Optimum" technique*				
		Continuous occlusion		*Intermittent occlusion*		
		Artery	*Pedicle*	*Artery*	*Pedicle*	*Manual compression*
48	35±5	8	2	2	16	20

with controls until day 5. On day 5, however, all ischaemic groups exhibited a highly significant increase in intracellular water (Fig. 2) and radioactivity index (Fig. 3), the increase being most evident when intermittent clamping of the renal artery or renal pedicle or manual compression of the renal cortex was the technique used. By day 10 only those kidneys rendered ischaemic by continuous renal artery clamping did not exhibit a significant increase in intracellular water or radioactivity index. Even by day 20 a persistent significant increase in intracellular water and radioactivity index was detectable if either intermittent renal pedicle clamping or manual compression had been employed to produce temporary ischaemia.

Discussion

Although it is almost 100 years since Litten's (1880) original observations on the effect of varying periods of ischaemia on the kidney, there is still a considerable divergence of opinion as to the least damaging technique to be used for temporary control of blood flow. This was demonstrated by a survey we conducted into the technique preferred by a group of consultant surgeons, all of whom were experienced in conservative renal surgery (Table 1).

In view of our experimental findings it is of particular interest that the majority favoured either intermittent clamping of the renal pedicle or manual compression of the renal cortex to produce temporary ischaemia, an opinion advocated most notably by Semb (1956). Although inulin clearance studies indicate that transient continuous renal artery clamping evokes less functional disturbance, they are too insensitive to compare accurately the renal damage inflicted by the various techniques used for the brief warm ischaemic times employed in clinical practice.

On the other hand, Leary *et al.* (1963), using a 2 h warm ischaemic time in the dog kidney, found inulin clearance was normal 15 days after continuous renal artery clamping, whereas after intermittent renal artery or pedicle clamping inulin clearance remained severely depressed after 45 days.

We conclude that if it is necessary to interrupt temporarily the renal blood flow in the course of conservative renal surgery, continuous clamping of the renal artery is the method of choice.

Acknowledgements

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The Pattern of Urolithiasis in the Sudan

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Summary—Vesical stones in children are the commonest stones in the Sudan. In recent years there has been a progressive increase in the number of operations for upper tract stone, suggesting a change in the pattern of urolithiasis.

The Northern third of the Sudan comprises hot, dry desert which gradually merges into the hot, humid equatorial Southern third. This paper assesses the present pattern of urolithiasis in the country and the changes which have occurred in this pattern over 40 years.

Material and Procedure

During the 5-year-period 1965-1969 information was obtained from 8 major hospitals scattered across the country. The period of time over which information was available varied from 2 to 40 years. Data were obtained on the total number of surgical operations performed as well as on the number performed for urinary calculi, including age, sex and location of the stone in the urinary tract (Table 1).

Results

Figure 1 shows the number of operations for stones expressed per 10,000 surgical operations. Seventy-two per cent of operations were for lower tract stones and the majority of these were in children. Ninety-five per cent of lower tract stones and 75% of upper tract stones occurred in males. Only in Juba in Southern Sudan is there a low incidence of stone.

Figure 2 shows the operations for stones in the 3 major hospitals in Khartoum province for the 40-year-period 1931-1970. The progressive increase in operations for stones was more marked in the upper tract and rose from 1:6 during 1931-1940 to 1:1.4 during 1961-1970.

Discussion

The data presented indicate that while stone formation is relatively common in all the Northern provinces of the Sudan, it is rare in the Southern region. Lower urinary tract stones, usually from male children in rural areas, comprised more than two-thirds of all stones. Similar patterns have been described in India (Ramalingaswami

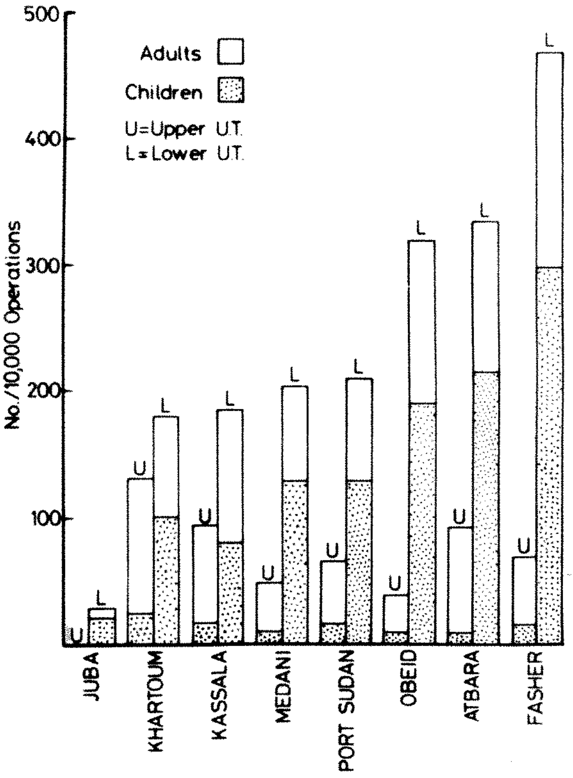

Fig. 1 Incidence of operations for calculi in the provincial hospitals.

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Table 1 Urinary Calculi in the 7 Provincial Hospitals 1965-1969

	Lower urinary tract stones		*Upper urinary tract stones*	
	Children (below 16 years)	*Adults*	*Children (below 16 years)*	*Adults*
Number of patients	360	247	47	195
Percentage	42.4%	29%	5.5%	23%
Males	95%		75%	
Females	5%		25%	

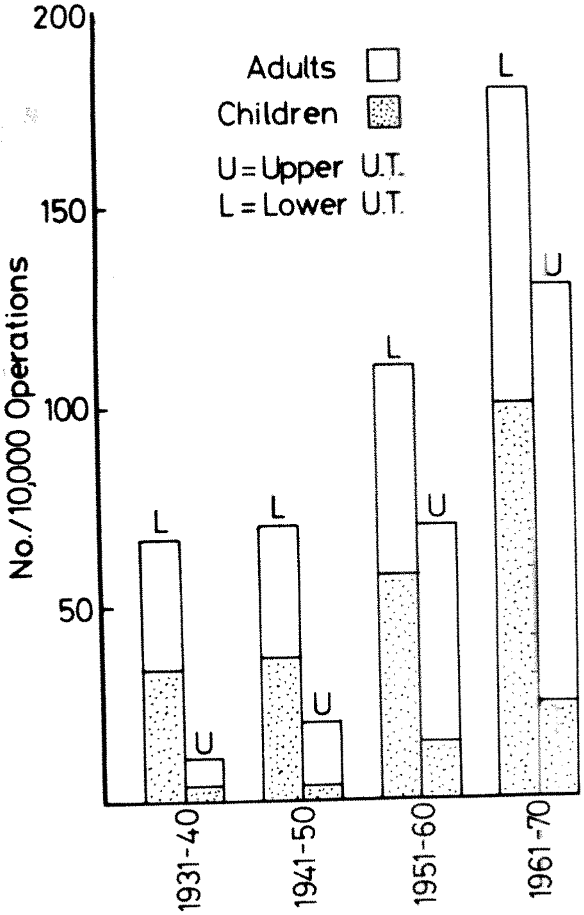

Fig. 2 Incidence of operations for calculi at Khartoum hospitals 1931-1970.

and Aurora, 1961) and in South-East Asia (Westermeyer, 1971). In the Sudan the increase in the relative number of operations for urolithiasis represents a true increase.

In Western Europe, Andersen (1969) described the gradual change from predominance of lower urinary tract stones to upper tract stones. It is quite probable that in urban populations, such as that in Khartoum, the pattern of urolithiasis is approaching the modern pattern in that lower tract stones are becoming uncommon while upper tract stones are progressively increasing. Further observations will be awaited to show whether upper tract calculi will ultimately become predominant. Moreover, parallel studies of the incidence of urolithiasis in urban and rural communities, rather than the study of hospital records, will show more clearly the pattern of urolithiasis in each community and the changes that may occur in the pattern.

Acknowledgement

Acknowledgement is made to all surgeons who have kindly and willingly supplied the data from their operation records.

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Uretero-Neo-Cystostomy in Renal Transplantation. Is An Antireflux Mechanism Mandatory?

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Summary—We report a retrospective analysis of 120 kidney transplantations in which a simple end-to-side ureteric implantation in the bladder without antireflux mechanism was made. From this study no greater incidence of vesico-ureteric reflux could be demonstrated and, even when present, reflux neither interfered with graft function nor caused an increased incidence of recurrent urinary tract infections. The incidence of other urological complications (leakage, obstruction) being equal, this very simple technique yielded in our hands the best results and we recommend its use in kidney transplantation.

Restoration of the continuity of the urinary tract in kidney transplantation may be achieved either by a high anastomosis (pyelo-ureterostomy or uretero-ureterostomy) or by a low ureter-bladder anastomosis. Uretero-neo-cystostomy is usually preferred in view of the associated lower frequency of complications. A review of the literature (Debruyne, 1977) revealed 10% urological complications with uretero-neo-cystostomy compared to 20% for the high anastomoses. The ureter is implanted in the bladder usually with an antireflux mechanism, either by means of an external uretero-neo-cystostomy as described by Lich *et al.* (1961) and Grégoir (1964) or transvesically with a submucosal tunnel (Politano and Leadbetter, 1958). Little is known about ureteric implantation without antireflux mechanism where the donor ureter is anastomosed end-to-side to the bladder. Several small series have been published (Franksson *et al.*, 1968; Ackerman *et al.*, 1970; O'Donoghue *et al.*, 1971; Piza *et al.*, 1973; Whittier *et al.*, 1974) but data on post-operative follow-up studies are scarce. A direct implantation is the easiest technique to perform. It was used almost exclusively in the early years of transplantation but was abandoned when antireflux surgery became accepted in general urological practice.

In a retrospective study of a series of kidney transplantations in which the ureter was implanted into the bladder without an antireflux mechanism we have determined the incidence of reflux and examined the effect of reflux on the allograft.

Material and Methods

One hundred and eighty-eight kidney transplantations were performed from 1968 to 1977, but in order to have a minimum follow-up period of 1 year only 154 transplantations, in 143 patients, are included in this study. In 134 cases the ureter was implanted into the bladder; this was done 14 times with a submucosal tunnel and 120 times (in 112 patients) as an end-to-side anastomosis, without an antireflux mechanism. We also performed 1 uretero-ureterostomy, 16 pyelo-ureterostomies and 3 uretero-ileostomies.

Operative Technique

After distending the bladder with 200 to 300 ml of sterile 0.9% sodium chloride, its lateral wall on the side of the allograft was prepared free by blunt dissection. The bladder was then opened at the fundus and the inferolateral bladder wall bluntly perforated very close to the trigone. The perforation was made as obliquely as possible to give the ureter a long intramural segment. The ureter was drawn through this perforation into the bladder, excess length excised, and a slit 0.5 cm in length made on its upper side. The ureter was then anastomosed to the bladder

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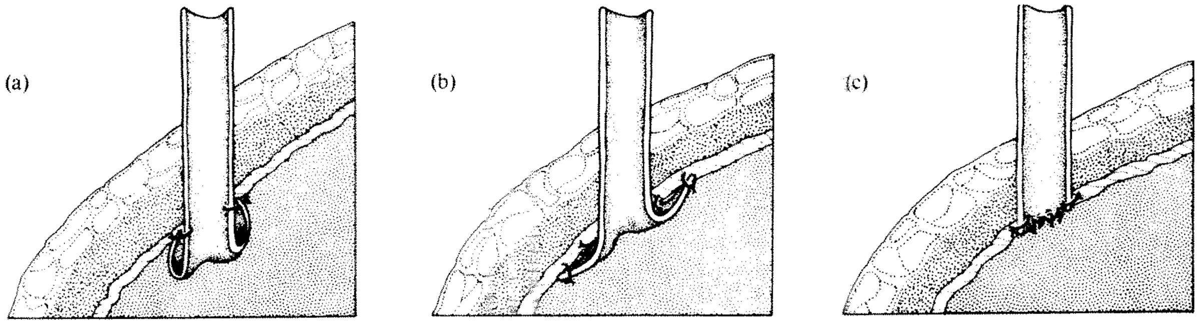

Fig. 1 Ureter-bladder anastomosis without antireflux mechanism: (a) with nipple, (b) fish-mouth and (c) end-to-side.

mucosa by interrupted plain catgut 3/0 sutures through the whole thickness of the ureteric wall (Figs. 1a, b, c and 2). In some cases the anastomosis was made over a fine tube. The bladder was closed in 2 layers and a urethral catheter was left for drainage.

Results

From the 120 allografts where the end-to-side anastomosis was used, 75 (62.5%) are still functioning well. The transplant failed in 45 patients and 23 of these died either in the early postoperative period or at a later date. Urological complications were responsible for only 1 death. Transplant nephrectomy was necessary in 22 patients because of either vascular complications or because of rejection and in only 1 patient because of urological complications (leakage). Fourteen transplants (11.6%) were associated with urological complications. These were leakage of urine in 10 cases and obstruction in 4 cases.

Reflux was found in 7 (10%) of the 70 patients in whom 1 or more micturating cystograms were performed in the follow-up period. In most cases the reflux was of a mild grade and present only during micturition. The morbidity it caused was minimal and reimplantation was never necessary. All 7 patients have normal intravenous pyelograms. Three months after transplantation 2 of the 7 patients had a urinary tract infection. In 1 of these the infection was easily treated with antibiotics. The other patient had an asymptomatic bacteriuria but this was not associated with any deterioration of kidney function and the IVP remained normal (Figs. 3a and b).

In 63 patients without reflux, 12 patients (19%) had urinary tract infections after 3 months. The group consisted of 9 women and 3 men. Most of these infections were easily treated with antibiotics. One male with chronic prostatitis had recurrent urinary tract infections and 3 women had an asymptomatic bacteriuria that was resistant to treatment.

Discussion

From these results it appears that reflux, as diagnosed by radiological methods, occurs only in a minority of transplanted patients even when the ureter is implanted without an antireflux mechanism. The real incidence of reflux, how-

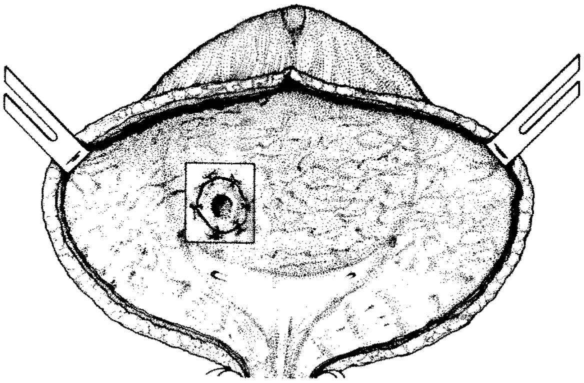

Fig. 2 Intravesical view after ureter-bladder anastomosis; site of the uretero-neo-cystostomy without antireflux mechanism.

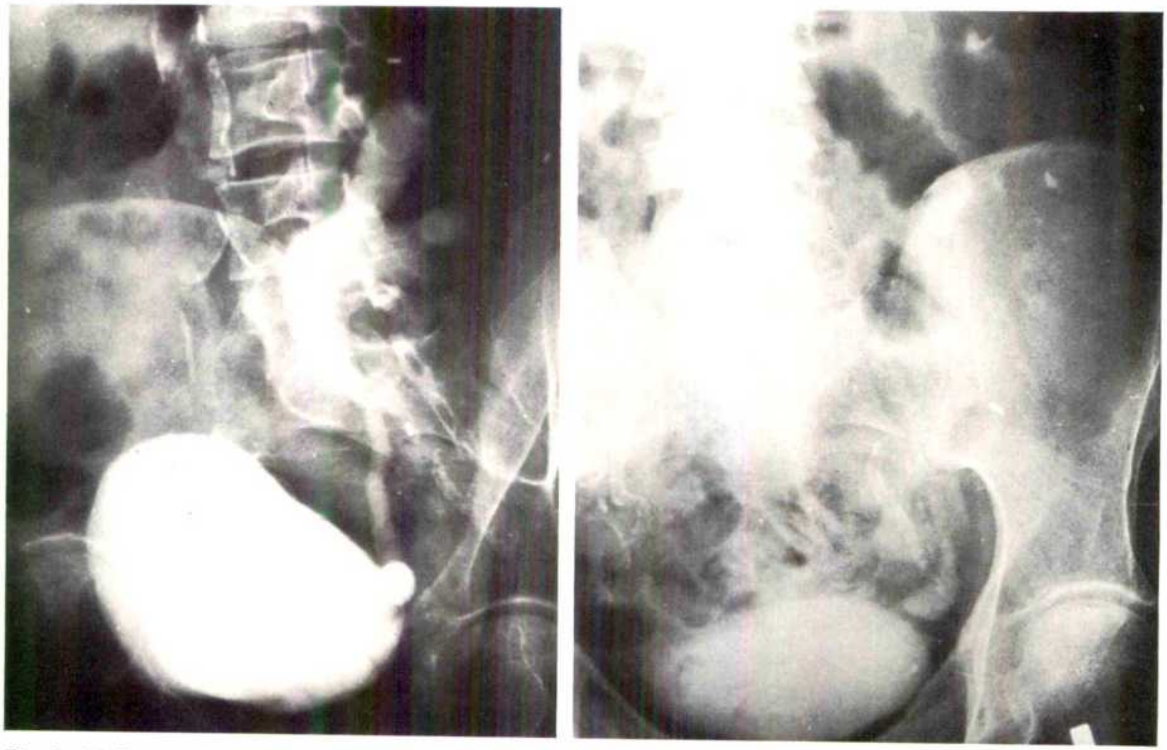

Fig. 3 (a) Cystography: vesical reflux in the allograft kidney. (b) IVP shows good kidney function and unobstructed evacuation of the dye.

ever, could be higher since a mild degree of reflux in a normal ureter can be easily missed on routine cystography. Few data are available in the literature on the incidence of reflux since the follow-up of transplantation patients does not include routine micturating cystography.

Although a similar incidence of reflux occurs after ureteric implantations with or without antireflux mechanism, the reported incidence is variable. A mean incidence of vesico-ureteric reflux of 12.1% was found in the published series (Table 1) where the ureterovesical anastomosis was performed with a submucosal tunnel. This figure is very similar to the figure of 14.2% in those series where the ureter was reanastomosed without antireflux mechanism. Nevertheless, there are great differences in the results reported by several authors using the same technique.

The incidence of 50% reflux as seen by Powis *et al.* (1971) as well as the 20% reflux encountered by Konnak *et al.* (1975) contrast with the low incidence found by de Campos Freire *et al.* (1974). This latter group used a submucosal tunnel, whereas the 2 former groups used a short tunnel to avoid stenosis. Rees and Williams (1972) are the only authors who reported a significant difference in the incidence of reflux between implantations with and without antireflux mechanism. Other authors (O'Donoghue *et al.*, 1971; Whittier *et al.*, 1974) did not find such a high incidence of reflux using the oblique ureteric implantation. This is confirmed by the results in our study and may be explained by the fact that the bladder wall in dialysis patients (especially men) is frequently thickened, so that it would seem reasonable that the more oblique course of the ureter in the bladder musculature is sufficient to prevent reflux.

It remains to be considered whether reflux is deleterious to the allograft. We do not doubt that reflux of infected urine is damaging to the kidney and a cause of acute and chronic pyelonephritis. On the other hand, it is doubtful whether reflux of sterile urine is damaging to the kidney and whether it plays a role in the development of urinary tract infections. It seems likely that the anatomical integrity of the papillae is more important than the reflux of sterile urine.

Table 1 Incidence of reflux in kidney transplantation

	Number of patients	*Incidence of reflux*	*Percentage*
1. *Ureter-bladder anastomosis with submucosal tunnel*			
Powis *et al.* (1971)	20	10	
Rees and Williams (1972)	15	1	
Urquhart-Hay *et al.* (1974)	20	1	
Clunie *et al.* (1974)	34	5	
de Campos Freire *et al.* (1974)	88	1	
Konnak *et al.* (1975)	50	10	
Total	227	28	12.1
2. *Ureter-bladder anastomosis without submucosal tunnel*			
O'Donoghue *et al.* (1971)	56	2	
Rees and Williams (1972)	9	8	
Whittier *et al.* (1974)	13	4	
Own series	70	7	
Total	148	21	14.2

The convexity of the papilla neutralises the high hydrostatic pressure wave and thus prevents intrarenal reflux. As repeatedly demonstrated, intrarenal reflux is the cause of pyelonephritic scarring, be it by the high pressure of sterile urine or, in the case of infected urine, by massive intratubular invasion of micro-organisms (Rose *et al.*, 1975; Bourne *et al.*, 1976). This explains why reflux, without urinary tract infection, can lead to renal failure (Salvatierra *et al.*, 1973; Bakshandeh *et al.*, 1976). The existence of the papillary antireflux mechanism has clearly been demonstrated experimentally (Ransley and Risdon, 1974). Damage to the papillae can be produced by chronic obstruction, infections and necrosis of the papillae or be present as a congenital anomaly. This is not the case in kidney transplantation. The allograft is in principle a normal kidney with undamaged papillae. A mild degree of reflux therefore cause no appreciable damage to the kidney, especially in the presence of good diuresis.

The possible relationship between reflux and glomerular lesions (Mathew *et al.*, 1977) needs further study before firm conclusions can be drawn.

It is difficult to determine whether reflux in transplant patients is responsible for the development of urinary tract infections. Metyš *et al.* (1975) found no significant differences in patients with or without reflux. Powis *et al.* (1971) on the other hand found a correlation, but they studied only 13 patients. Yadav *et al.* (1972) reported a higher incidence of urinary tract infections in transplant patients with reflux. In 4 of their 28 patients they even had sufficient reason to incriminate reflux as the cause of deterioration of kidney function. In a prospective study of 29 transplantations without antireflux tunnel, Whittier *et al.* (1974) could not confirm these findings. We were also unable to detect a higher incidence of urinary tract infections in our patients with reflux, and besides this the infections that occurred were easily controlled irrespective of the presence or absence of reflux.

Finally, no greater frequency of urological complications was seen. The incidence of 11.6% urological complications (14 of 120 patients) is similar to the 10% associated with implantations of the ureter with submucosal tunnel as collected from the literature: 472 urological complications in 4787 transplantations (Debruyne, 1977).

In view of these results it seems justifiable to recommend this simple method of ureter implantation in kidney transplantation.

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Reimplantation of the Wide Ureter

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Summary—A modification of the technique of Politano and Leadbetter for reimplantation of wide ureters is described. Nine patients with obstructive megaureter (10 ureters) and 6 with gross vesicoureteric reflux (9 ureters) were treated. A satisfactory result was obtained in 6 of the obstructed patients (7 ureters) and ultimately, after re-operation, in 1 of the remaining ureters. Reflux was corrected in all 6 patients. This method requires less extravesical dissection than others involving extensive remodelling of the wide ureter. There is therefore less risk of damage to the distal ureteric blood supply and the natural flap valve mechanism at the ureteric orifice may be more effectively emulated.

Antireflux surgery on ureters of normal calibre is usually successful. The technique of Politano and Leadbetter (1958) is frequently used with one or other minor modification (Clark and Hosmane, 1976), though simple advancement (Cohen, 1977) is also often satisfactory. However, reimplantation of the wide ureter caused by vesicoureteric reflux or idiopathic obstruction has had a sinister reputation. A variety of techniques has been used to narrow the calibre. For example, Paquin (1959) constructed a cuff at the site of reimplantation. On the other hand, Hendren (1969) has adopted a more radical approach with extensive re-modelling of the ureter through most of its pelvic course.

We present another technique which has the virtue of simplicity, avoids extensive dissection with possible damage to the blood supply to the ureter and attempts to reconstruct the natural flap valve mechanism at the ureteric orifice.

Patients and Methods

Fifteen patients (aged 9-52 years at presentation) were studied. They all had wide, tortuous ureters and the majority (9) were obstructed at the lower end whilst the remainder had vesicoureteric reflux. In 1 case this was due to tuberculosis, but the majority of patients with obstruction had a short narrow distal fibrotic segment with muscle hypertrophy and occasionally squamous metaplasia of the mucosa. These features may be regarded as typical of primary idiopathic obstructive megaureter. The abnormality was bilateral in 1 patient.

Most patients presented with loin pain. One 22-year-old male was investigated pre-operatively for severe hypertension. Another patient had bilateral obstruction with scarring of the kidneys and renal calculi.

Of the 6 patients with reflux, 3 had bilateral megaureters. Overall renal function in 3 patients was poor (creatinine clearance < 20 ml/min). One of the patients with unilateral reflux evidently acquired incompetence of the vesicoureteric junction after diathermy incision of a ureterocele. All patients with vesicoureteric reflux presented with recurrent urinary infections.

Technique (Figs. 1a-c)

A combined intravesical and extravesical approach is used to mobilise the ureter. An umbilical catheter inserted and sutured into place in the ureter facilitates the intramural dissection. When present, the narrow distal segment found in idiopathic obstructive megaureter is resected. A long 'V' is then excised from the ureter. This is then sutured to narrow the ureter, leaving the terminal 1 to 2 cm to form a 'Y' (Fig. 1a). Saline is injected to develop the submucosal plane in the bladder and facilitate formation of a tunnel. The reconstructed ureter is drawn through a new hiatus in the detrusor and the submucosal tunnel (Fig. 1b). The lower edge is sutured to the bladder mucosa, leaving the defect in the distal ureter covered by

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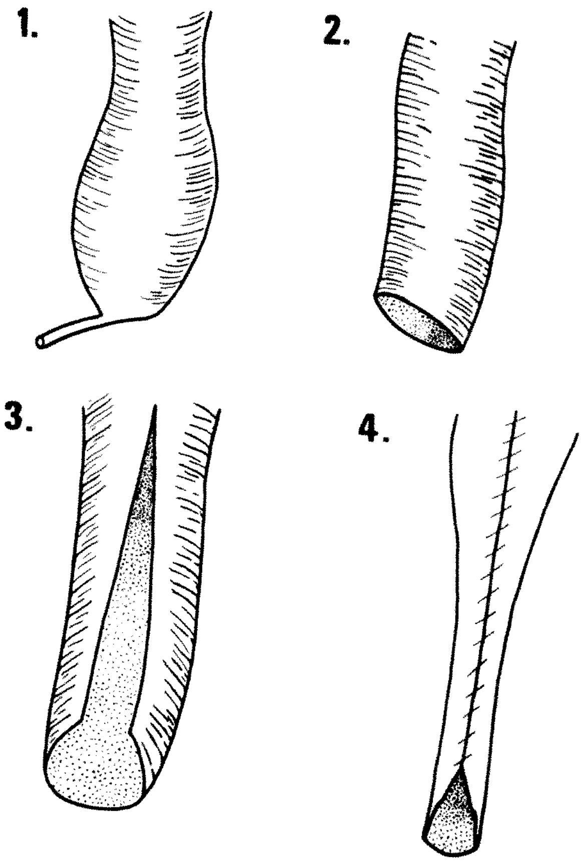

Fig. 1a Technique for reconstruction of the lower end of the ureter. In patients with obstructive megaureter the distal segment is excised.

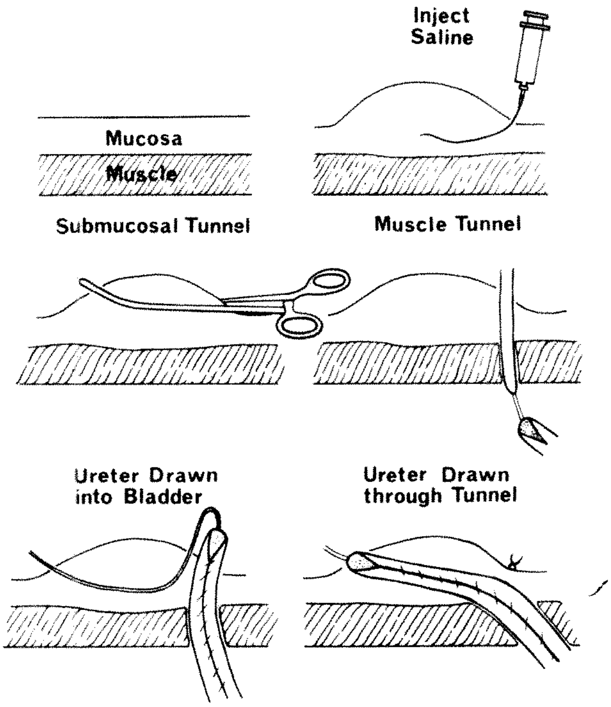

Fig. 1b Modified Politano-Leadbetter technique (intravesical and extravesical approach) for reimplantation of the reconstructed ureter.

a bladder mucosal flap (Fig. 1c). This acts as a flexible valve to prevent reflux. The neocystostomy is not usually splinted and the bladder is drained with a fine catheter for 5 days.

Results

Obstruction

All 9 patients were assessed post-operatively. A satisfactory result was obtained in 6: the excretion urogram showed definite improvement in terms of concentration and pelviureteric dilatation (Fig. 2); the micturating cystourethrogram showed no relux and the urine was sterile. There was no recurrence of symptoms. Of the remaining 3 patients, 1 had persistent hypertension and probably a degree of residual obstruction; 2 patients required re-exploration and further reimplantation but in 1 of these the ureteric anastomosis was healthy and intact, the obstruction being proximal to the orifice and due to kinking above the hiatus in the detrusor.

Reflux

Reflux was corrected in all 6 patients. Postoperative X-rays showed improvement in pelviureteric dilatation in 3 patients. Two female patients had recurrent urinary infection; in 1 this had not been a feature of the pre-operative course. In 3 patients with poor renal function (creatinine clearance < 20 ml/min) deterioration was not affected by reimplantation and long-term dialysis treatment was ultimately required.

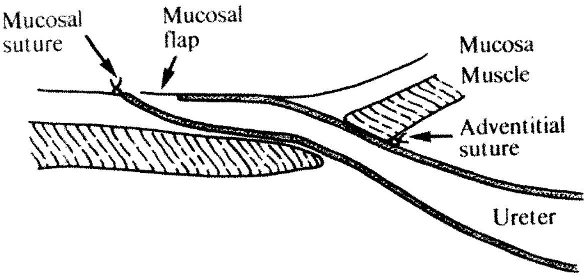

Fig. 1c Completed ureterovesical anastomosis showing free flap of bladder mucosa.

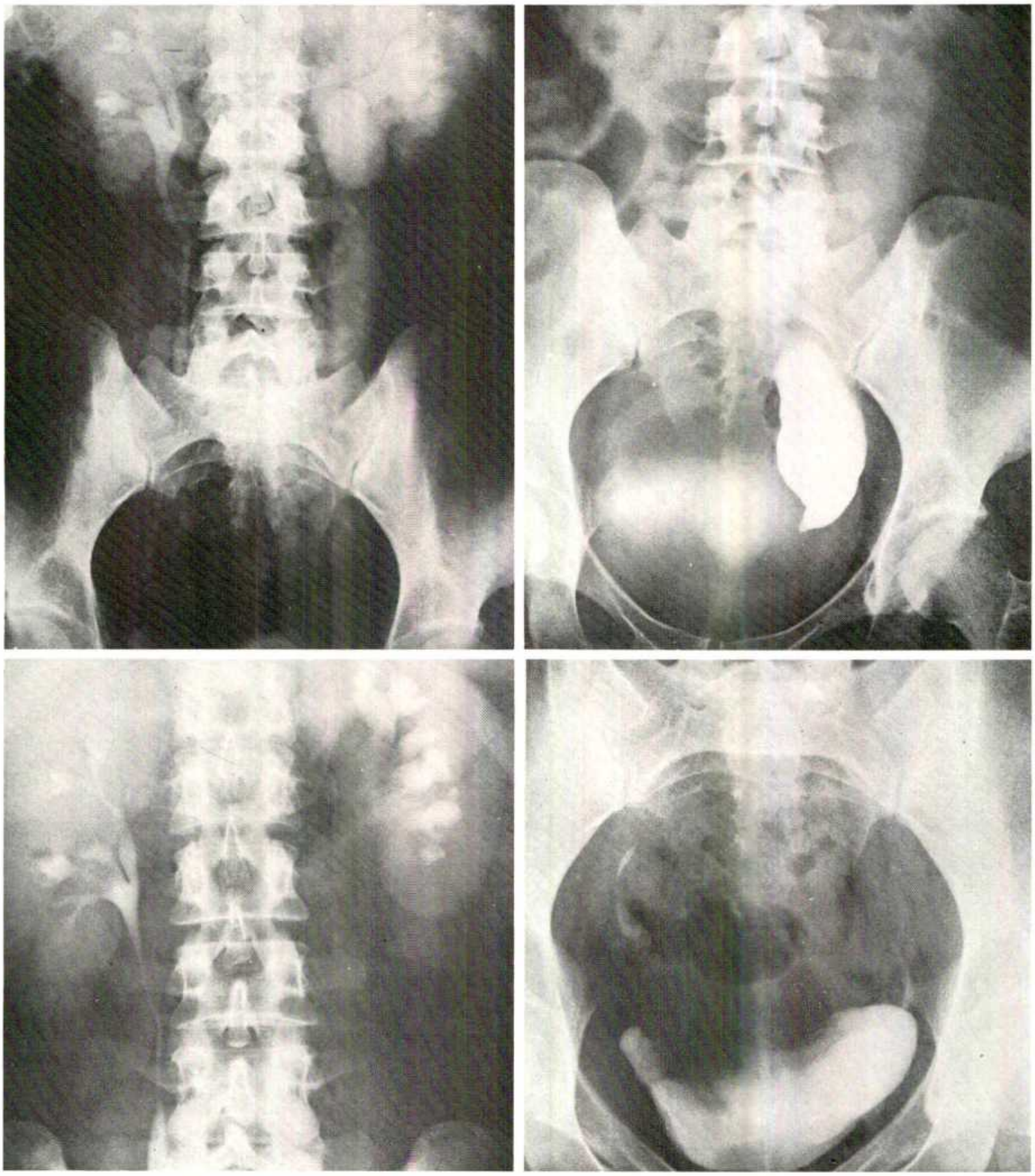

Fig. 2 Patient C.R. (a) IVU: 30 min after injection (40 ml 45% Hypaque). Pre-operative film. (b) Left retrograde pyelogram. Pre-operative film. (c) IVU: 10 min after injection. Eighteen months after operation. (d) IVU: 45 min after injection. Eighteen months after operation.

Discussion

Whether renal function will remain stable or will deteriorate in cases of vesicoureteric reflux or idiopathic obstructive megaureter is difficult to predict, particularly when presentation is in the older child or adult. The interrelation between the urodynamic disorder of the upper tract and other factors such as infection is obscure and this has led to uncertainty about clinical management. In the past it was felt that a conservative approach was justified (Nesbit and Withycombe, 1954) but with improved technique it is now clear that surgical treatment may be more appropriate (Johnston, 1967; Williams and Hulme-Moir, 1970).

Broadly, the aim in surgical management has been to reduce the calibre and redundant length of the ureter and to reimplant it, after reconstruction, into the bladder (Hendren, 1969). Provided that a normal width of the terminal ureter has been achieved, the technique of Politano and Leadbetter (1958) is satisfactory. Their method depends upon construction of a submucosal tunnel of adequate length to maintain competence of the ureteroneocystostomy by reproducing the flap valve mechanism (Sampson, 1903). If the terminal ureter is too wide there may be difficulty in constructing a submucosal tunnel of adequate length. The preliminary tailoring and tapering of the supravesical ureter is therefore all-important. The risk of damage to the blood supply of the ureter during this process should not be underestimated.

We have modified the standard technique so that less manipulation of the ureter is required. Sufficient ureteric wall is removed from the terminal segment to construct a long 'V'. With the formation of a free flap of bladder mucosa acting as an antireflux mechanism in its own right, the length of the submucosal tunnel may be less critical.

The results suggest that the antireflux effect was always satisfactory. Stenosis recurred in 2 patients who were re-explored. However, kinking of the ureter had occurred above the anastomosis and was probably due to excision of an insufficient length of distal ureter. In all cases the anastomosis appeared to be healthy and with an intact blood supply. A few patients had occasional episodes of urinary infection post-operatively but these were always easily treated and there was no evidence that the upper urinary tract was involved. In any case it is controversial whether antireflux surgery affects the incidence of urinary infection (Fair and Govan, 1976) and observations on sterility of post-operative urine may not necessarily reflect on the effectiveness of the surgical procedure. The slow deterioration in renal function in 3 patients, despite treatment of their vesicoureteric reflux (P.S., N.M., D.N.) probably indicated that renal parenchymal damage was irreversible and unlikely to be affected by surgery. Reimplantation of the ureter in patients with a creatinine clearance below 20 ml/min is probably rarely indicated.

The operative technique described here provides a free flap of bladder mucosa similar to the triangular flap ureteroplasty described in the experimental animal (Girgis and Veenema, 1965) and in the management of ureteric obstruction after antireflux surgery (Manley and Ferrell, 1975). We have found our results sufficiently encouraging to recommend its use in the primary treatment of megaureter.

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The Behaviour of the Bladder During Physical Activity

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Summary—The technical difficulties of obtaining reliable recordings of bladder, rectal and detrusor pressures from patients who are standing, walking or exercising have been largely overcome by a method described in this paper. The recordings help us to understand the behaviour of the lower urinary tract during physical activity and are of value in the diagnosis of urological problems, especially incontinence.

During urodynamic investigations bladder and abdominal pressure changes are measured almost exclusively in patients who are requested to remain still. For example, in cystometry the bladder of the supine patient is filled by either a urethral or a supra-pubic catheter and provoked so that any detrusor pressure response can be measured and studied. Frequently such provocation is repeated after moving the patient to a sitting or standing position. Urological symptoms, however, especially urinary incontinence, sometimes occur only during physical activity or changes in posture.

Existing pressure measuring systems, using liquid filled catheters which couple the pressure within the bladder to externally mounted transducers, are unsuitable because of the acceleration of the liquid within the system caused by movement of the patient or the equipment. To overcome this problem we have developed a system capable of measuring both bladder and rectal pressures in ambulant patients over a period of several hours. Detrusor pressure is obtained by subtracting the rectal pressure (which represents abdominal pressure) from the total bladder pressure.

This paper describes the method and presents a series of recordings which illustrate how the bladder, rectal and detrusor pressures of women respond to activities such as standing, walking, running, etc.

Method

Transducers convert pressures into electrical signals which are readily amplified, displayed and processed. Liquid filled catheters are frequently used to couple the pressure within the body to external transducers. To overcome some of the problems associated with this method of coupling Shelley (1965) developed an air-probe device, the clinical results of which were described by Warrell *et al.* (1963). Another type of air coupled system was developed by James (1971). In this instrument air replaces water in a balloon tipped catheter and by using a compliant balloon the undesirable sensitivity of the device to temperature changes is reduced. A more recent version of this instrument is shown in Figure 1 and some of its features have been described by James (1976) and Beatty (1976). A linear relationship exists between the pressure applied to the balloon and the voltage obtained from the monitoring unit to approximately 160 cm H_2O above atmospheric. The zero drift is usually less than 5 cm H_2O over a period of 4 h with a balloon and transducer at near body temperature. The

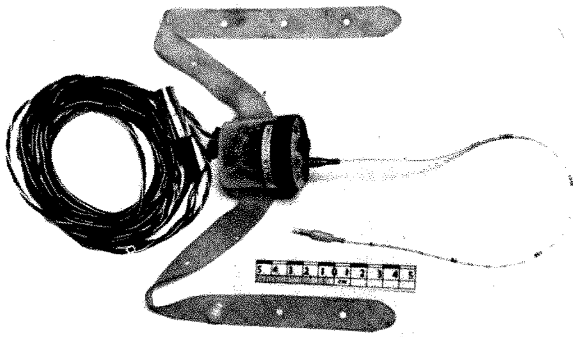

Fig. 1 The balloon, shown here with a diameter of 5 mm, is connected in a "flaccid" state. The transducer is strapped to the thigh of the patient and connected to the monitoring equipment with long leads.

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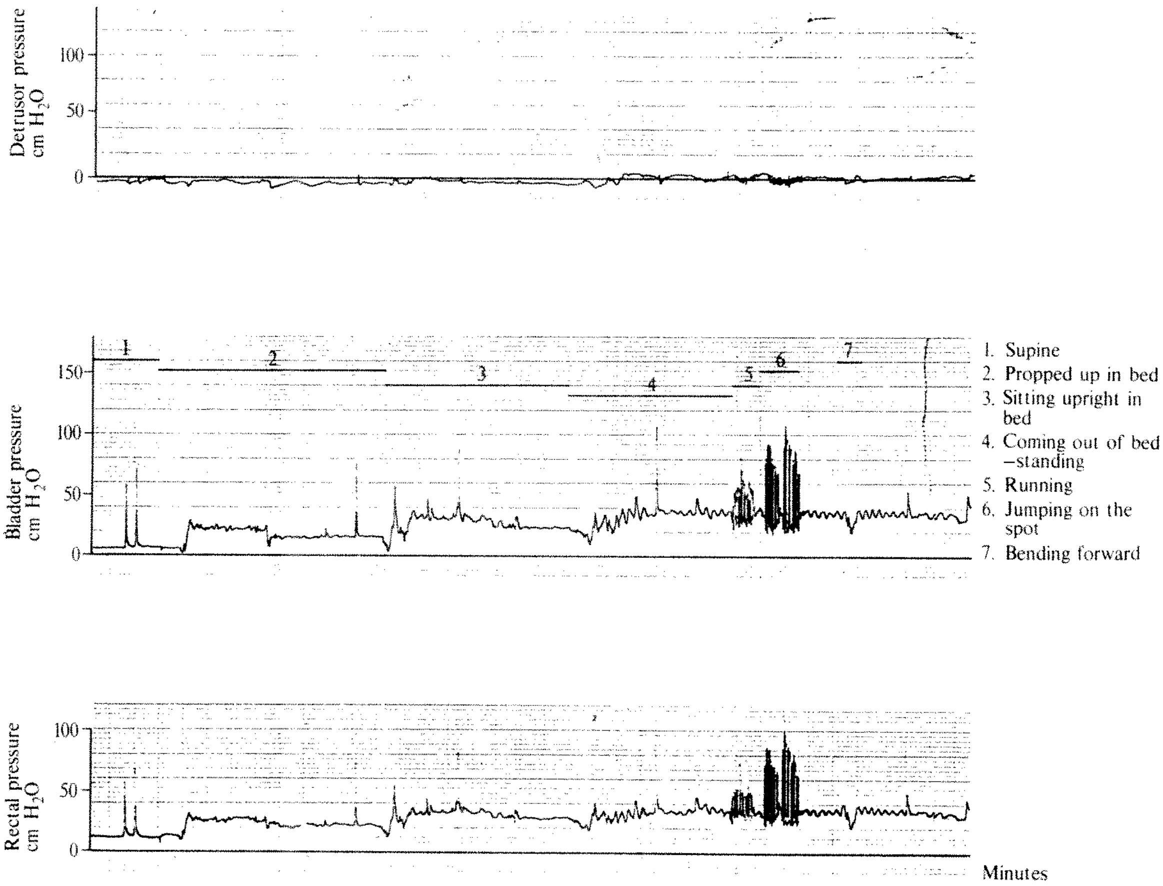

Fig. 2 A.B., aged 16. This recording shows the total bladder, rectal and detrusor pressure of a young and agile girl in the various stages of rising from bed. Large changes in pressure are seen during activities such as running and jumping. Pressure increases on coughing are shown in all postures and there is no significant change in detrusor pressure.

position of the catheter relative to the transducer is unimportant. This method is equally suitable for measuring rectal pressure, which is a convenient way of measuring changes in abdominal pressure. The detrusor pressure obtained by electronically subtracting the 2 signals from the 2 matched transducer systems is likely to be more accurate than that obtained when dissimilar catheters and transducers are used.

Using the apparatus described by James (1968), both manometer catheters are calibrated in sterile liquid against a mercury column. The bladder catheter is inserted transurethrally to a distance of about 6 cm in females and the transducer strapped to the thigh. The second transducer is attached to a catheter inserted about 6 cm into the rectum. Leads connecting the transducers to the monitoring and recording equipment are about 10 m long and restrict very little the activity of the patient.

Once this procedure is complete, patients can dress and are free to leave the bed and exercise. They are encouraged to engage in the exercises to which they are accustomed, *e.g.* sitting, standing, walking, running, jumping, lifting, etc. They can also micturate into a vessel which resembles a normal toilet but accommodates a flow rate sensor.

Results

The recordings (Figs. 2-8) have been selected from those obtained during the routine investigations of patients with urological symptoms, chiefly incontinence. Apart from 1 example (Fig. 4) there is no reason to believe, however, that they are

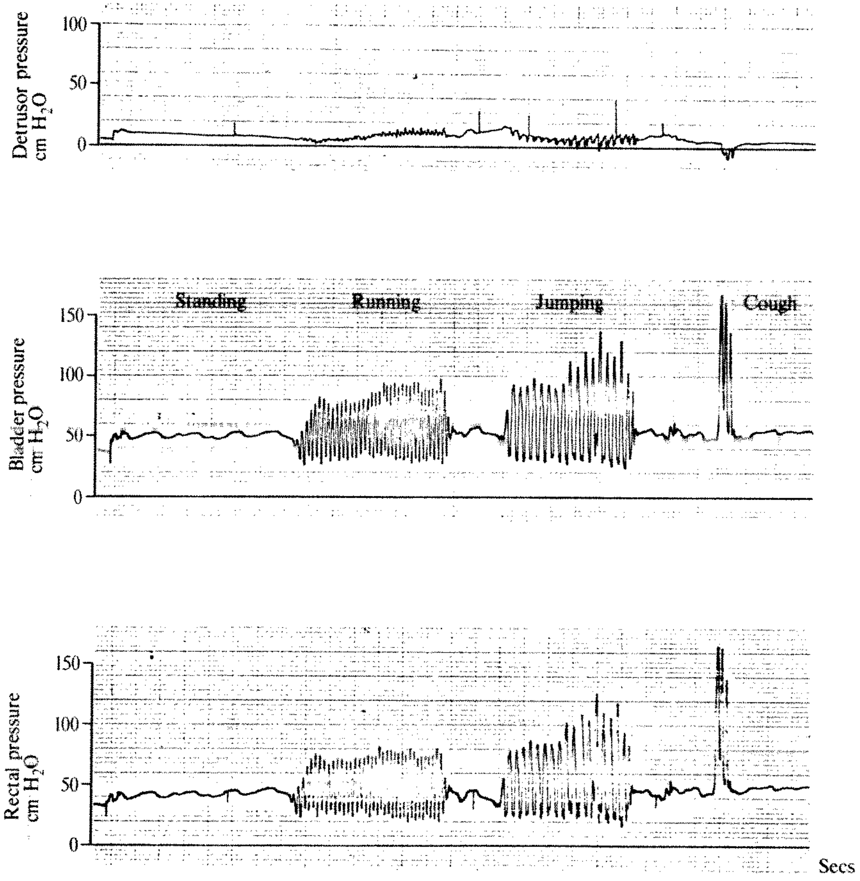

Fig. 3 P.G., aged 30. From these recordings it is clear that the major variations in pressure associated with these types of activities originate mainly from changes in intra-abdominal pressure. An explanation for the small changes in the subtracted pressure, seen particularly when the patient jumps, is not considered important.

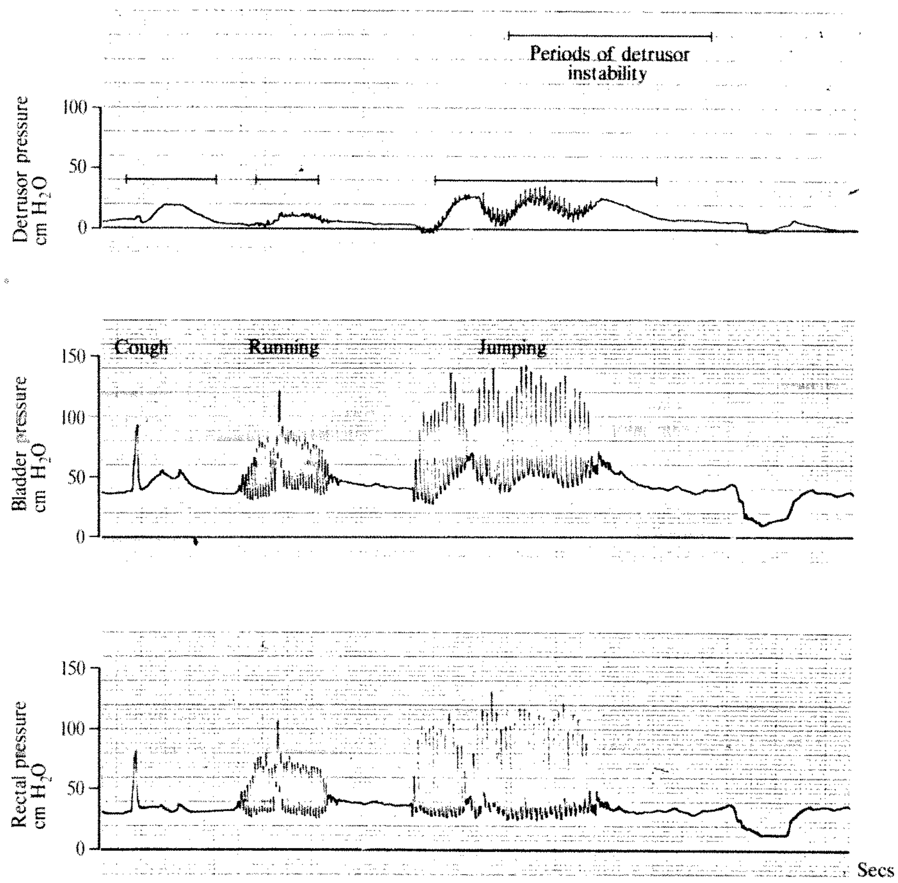

Fig. 4 M.D., aged 20. In this patient there is an increase of about 30 cm H_2O in detrusor pressure during the various exercises and also immediately following a cough. This is believed to be due to detrusor instability.

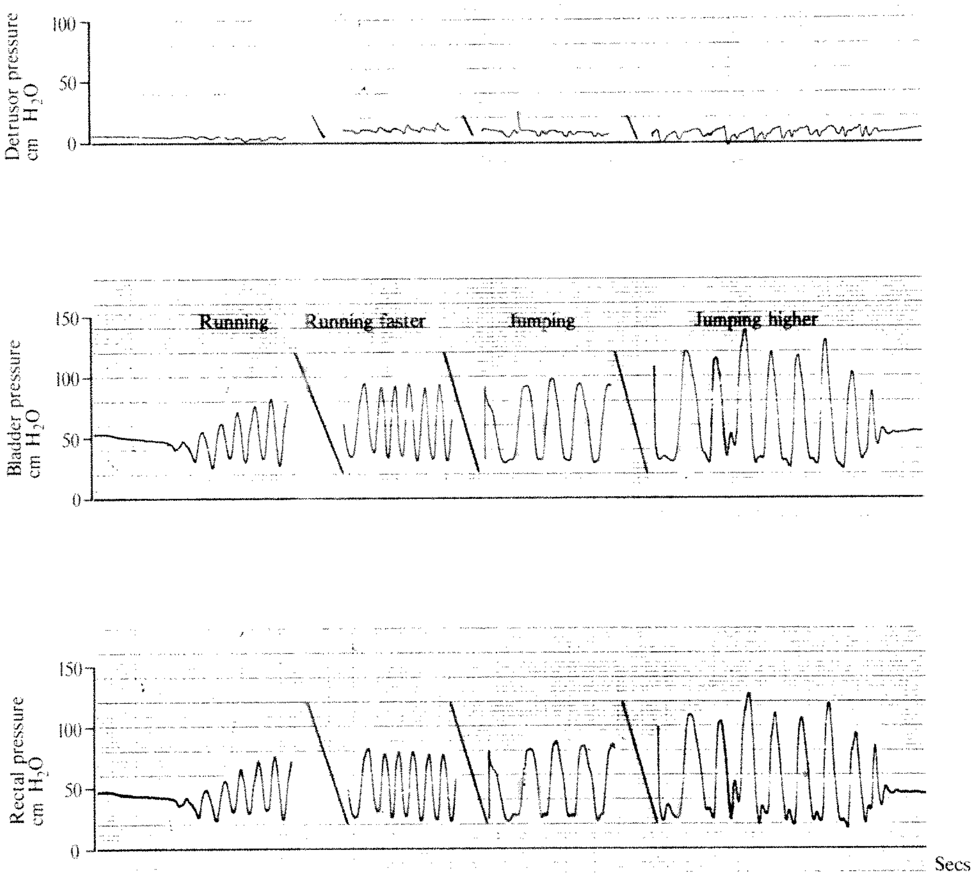

Fig. 5 P.G., aged 30. The repeated peaks in pressure coincide with the feet touching the floor during running and jumping. The effect of running faster and jumping higher is also shown. For present purposes the small changes in the subtracted detrusor pressure can again be ignored.

not typical of the physical behaviour of fairly normal bladders.

As is customary, detrusor pressure is obtained by subtracting the rectal pressure from the total bladder pressure. This produces consistent results provided that attention is focused only on the subtraction of the dynamic changes in pressure and not on the absolute values, which may often appear as a negative quantity and which may be due to the contribution of the resting rectal tone to the total rectal pressure. Inaccuracies in the matching of the 2 transducers and the electronic subtraction can also account for small changes in the subtracted detrusor pressure seen in some of the recordings; the shape of some of these changes suggests that they are not due to the detrusor itself.

Figure 2 shows firstly the measured bladder and rectal pressures of a young and agile girl rising through various stages from a supine to an erect position. The more erect her posture the more both pressures increase, and the total bladder pressure reaches a peak at about 40 cm H_2O on moving into the standing position. Running and jumping increase this pressure to a maximum of 90 cm H_2O, whereas bending over to touch the floor reduces the pressure by about 20 cm H_2O. The frequent "spikes" in pressure to 50 cm H_2O result from coughs. Most of these pressure variations are produced by changes in the abdominal pressure. During a period of sleep lasting about 20 min no measurable change in bladder or rectal pressure occurred. However, with the patient awake but never quite still, pressure variations of about 4 cm H_2O were recorded.

Rapid changes in both bladder and rectal pressures accompany running and jumping on the

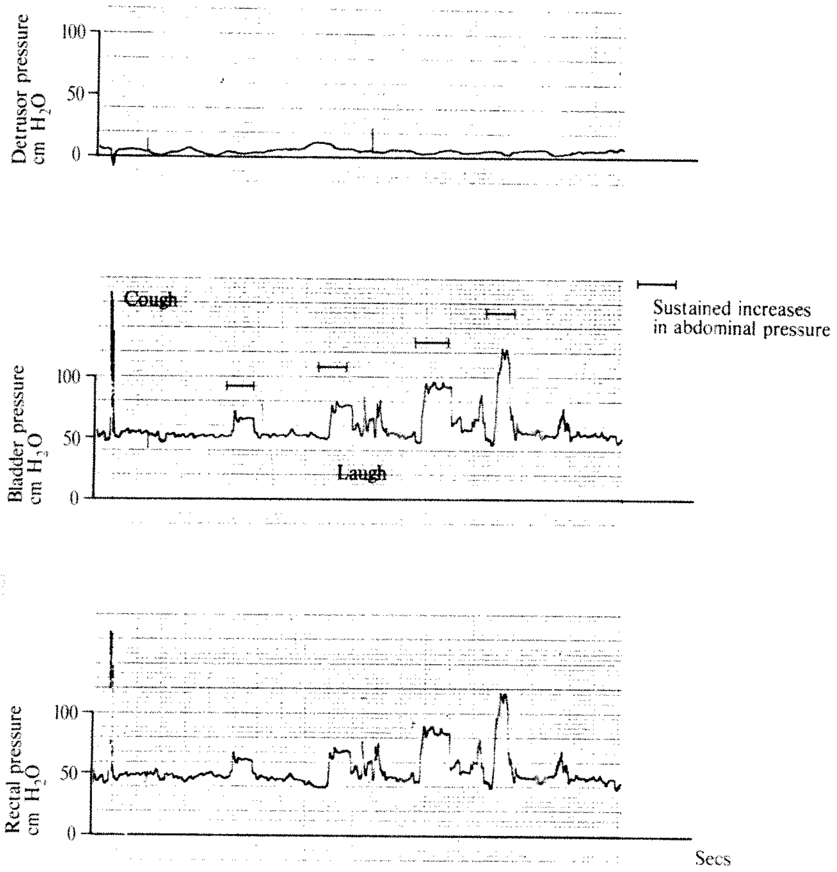

Fig. 6 P.G., aged 30. This shows the effect of sustaining an increased abdominal pressure over a period of several seconds. This occurs while blowing up a balloon and similar effects are occasionally recorded in patients with some respiratory problems.

spot (Fig. 3). The extent of the pressure rises is related to the fitness of the subject and the height of the jump. A "triple" cough momentarily increases both pressures by 120 cm H_2O; small changes in detrusor pressure are within the error range of the transducer systems.

Unlike the previous recording, Figure 4 shows marked detrusor activity following a cough and with running and jumping; the latter contributes about 40 cm H_2O to the total bladder pressure. Figure 5 shows in more detail and on an expanded time scale the same effect on bladder and rectal pressures with running and jumping. The cyclic variation or period is naturally different for both exercises, the peaks of pressure occurring when the feet touch the floor. The changes in the subtracted signal are small enough to be ignored.

To blow up a balloon by mouth needs abdominal effort and increases intra-abdominal pressure. Our experiments have shown that above certain levels abdominal and oral pressures are closely related. Patients can maintain oral pressure at or near the prescribed levels by blowing into a column of mercury or a meter (Fig. 6). This procedure produced pressure changes of almost 40 cm H_2O during laughter. During all of these activities the detrusor pressure remained substantially unchanged.

The similarity in records from both pressure channels is again seen in Figure 7 as the patient moves out of a chair into a standing position and coughs. During micturition there is an increase in the detrusor pressure due to its contraction. The effort required to get out of bed is greater for an obese patient (Fig. 8) than for a young girl (Fig. 2).

Discussion

The aim of this work has been to examine

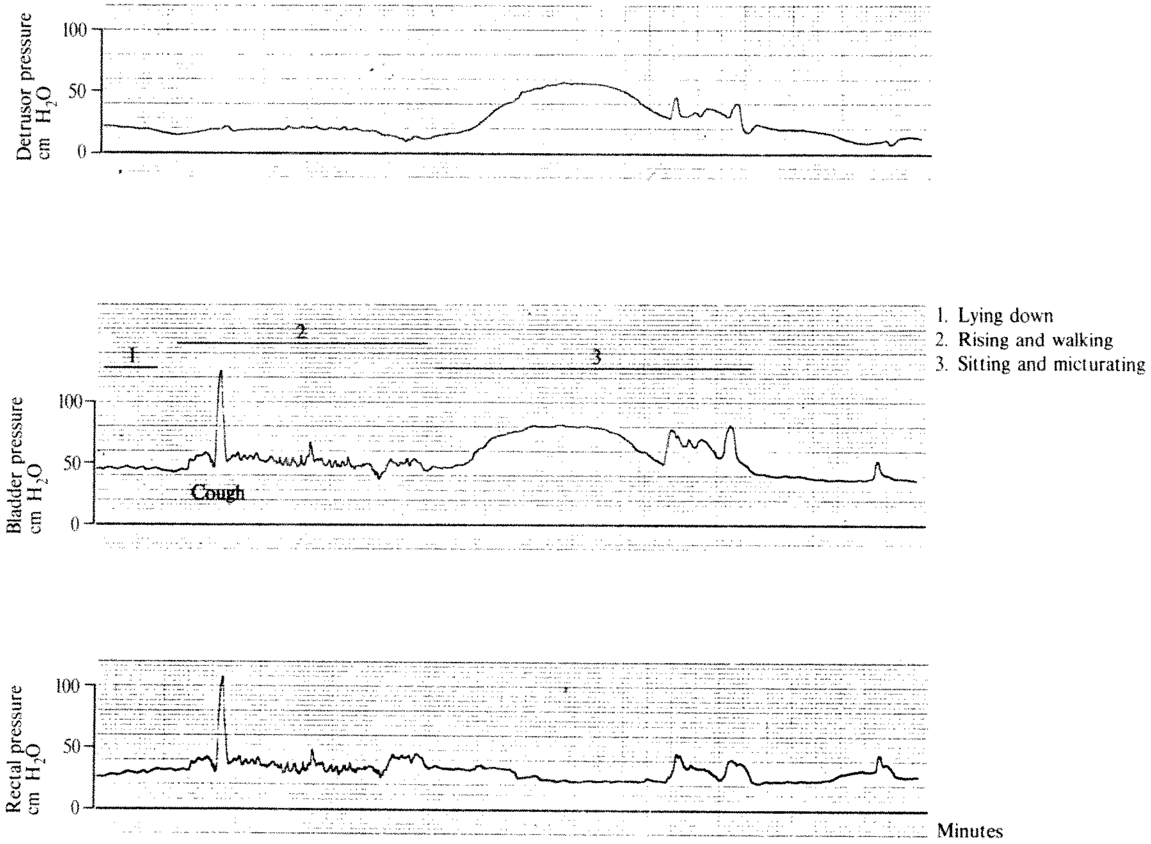

Fig. 7 N.D., aged 19. In this recording the patient stands up, coughs and then walks to the toilet. There is a marked change in detrusor pressure (note also some relaxation in the rectal pressure) during micturition, and on this occasion the patient voided 300 ml with a good uninterrupted stream.

a new method of measuring pressure in totally ambulant patients and to present a series of illustrations which are unique and which provide a better understanding of the mechanics of the lower urinary tract. The clinical background of the patients has not been presented and the clinical relevance of the method will be the subject of a further communication when further data are available.

The liquid coupled transducer system is unsuitable for obtaining satisfactory recordings in ambulant patients, but is a satisfactory method for measuring pressures in patients who remain still. The equipment is carefully set up and all air bubbles are removed from the liquid. Failure to comply with this procedure distorts the recording of rapid changes of pressure such as occur with coughing. Additional corrections of several centimetres of water will also be required when the tip of the catheter is moved above or below the external transducer. Proper calibration before each examination is recommended.

A new type of measuring catheter (the Millar catheter), which has overcome most of these problems, is available commercially. The sensing element is mounted on its tip and measures pressure at source. It was used in this clinic for some time, but its expense and high failure rate account for the revival of the air coupled balloon.

The recordings from the air coupled balloon confirm that total bladder pressure in ambulatory subjects is under the influence of intra-abdominal pressure, measured intra-rectally.

The difference between the maximum urethral pressure and the total bladder pressure is known as the closure pressure and, if it remains positive, urine will not escape along the urethra. Changes in abdominal pressure are not always transmitted equally to both bladder and urethra, and closure pressure is reduced (and in some instances

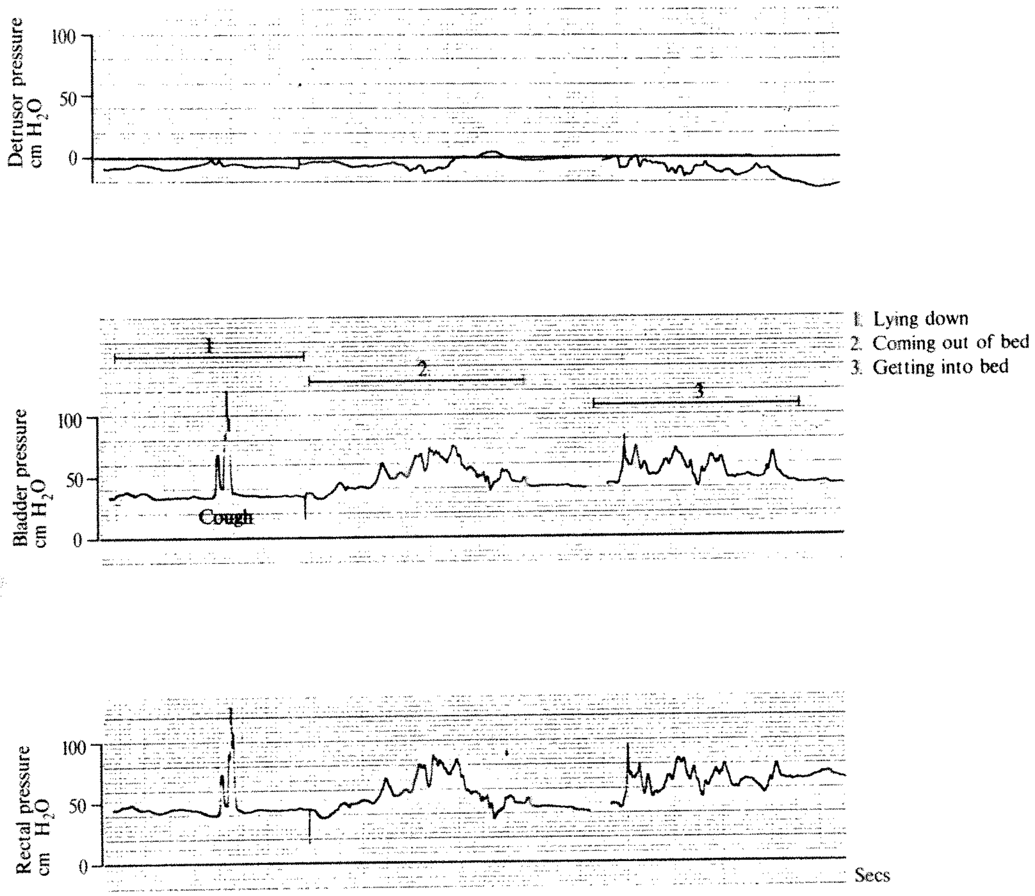

Fig. 8 B.W., aged 55. The effort required by this rather obese patient in rising out of bed results in much larger changes of pressure than the corresponding ones seen in Figure 2 for the agile girl. The subtracted pressure is a negative value, a possible explanation for which is given in the text. A poor closure pressure recorded while the patient was resting, coupled with a measured inadequate transmission of abdominal pressure to the urethra, accounted for loss of urine during the above manoeuvre.

becomes negative) during activities such as coughing and changing posture. The changes in total bladder pressure with tasks such as moving in and out of bed, sitting, standing, etc., vary from 1 subject to another because the effort required influences the abdominal pressure and depends upon the agility and general fitness of the individual. A closure pressure measured when the patient is resting may be sufficient to maintain continence under stress in some cases; others, especially the elderly, with the same value of resting closure pressure, may not be able to maintain an adequate closure pressure when performing routine tasks.

Physiological measurements on patients during normal activity can only enhance our present knowledge and contribute to diagnostic procedures. Data obtained by investigating patients in the traditional examination positions require careful interpretation because the patient is less likely to be at ease than during normal activity. Further work has been carried out in which the amount and frequency of urine loss and other parameters are measured simultaneously with the pressures described in this paper, and it is hoped that the behaviour of the urethra can be studied using techniques similar to those described.

Acknowledgements

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Bladder Neck Incision—A Treatment for Retention with Overflow in the Absence of Adenoma

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Summary—Twenty-five cases of outlet obstruction with decompensated bladders and minimal adenomatous enlargement were treated by transurethral bladder neck incision.

The results showed that bladder neck incision was as effective as transurethral resection of bladder neck and prostate and was a useful operation, especially for the elderly uraemic patient. There were no complications and operating time was considerably less than that required for a formal transurethral resection.

The operation should be reserved for cases of outflow obstruction with no or minimal adenomatous hyperplasia.

Mortality from prostatectomy varies with the age of the patient and increases markedly in the over-80 age group (Ashley *et al.*, 1971). Mortality also increases in the presence of uraemia, and when age and uraemia are combined the figure is even higher. The increasing use of transurethral resection has reduced the dangers of prostatectomy (Singh *et al.*, 1973), especially for patients with small adenomas, but transurethral operations require special training and experience.

Retention with overflow is often associated with a very small adenomatous prostate and sometimes with no observable adenomatous enlargement. In 32 consecutive cases of retention with overflow, 25 had minimal or absent adenoma. These cases have been treated by bladder neck incision and the results are presented.

Patients and Methods

Thirty-two consecutive cases of chronic retention were investigated by routine haemoglobin, urea and electrolytes, and excretion urography. The age range was 44 to 75 years. Rectal examination and subsequent cystoscopy revealed significant adenomatous enlargement in 7 cases and these were treated by transurethral resection in 6 cases and retropubic prostatectomy in 1 case with a benign adenoma weighing 136 g. The remaining 25 cases had no significant adenomatous enlargement and were treated by bladder neck incision.

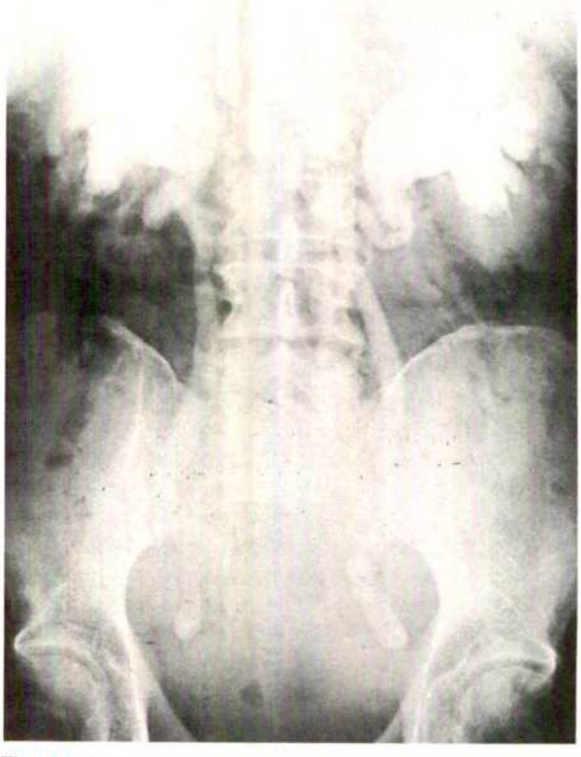

Fig. 1a Patient with retention with overflow and bilateral hydronephrosis and hydroureter.

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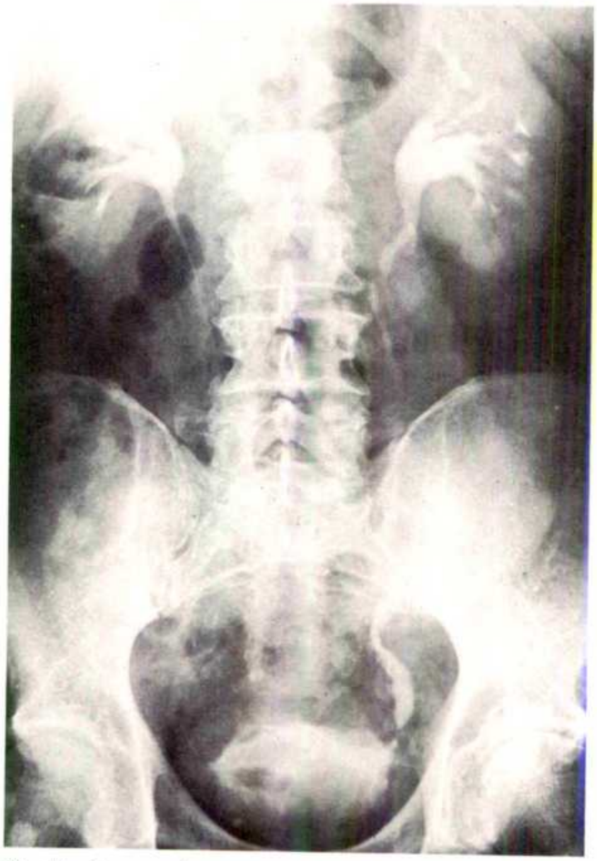

Fig. 1b Same patient 4 months following bladder neck incision. Hydronephrosis and hydroureter now resolved.

In the bladder neck incision group a urethral catheter was left *in situ* for 5 days. Urinary flow rates were measured approximately 2 months after operation. A post-operative urogram was requested again after a 2-month interval to assess residual urine and to observe any decrease in hydronephrosis and hydroureter.

Technique of Bladder Neck Incision

At cystoscopy the residual urine is measured and the bladder inspected for stone, tumour and inflammatory changes. The prostatic urethra is inspected and either the absence of adenomatous hyperplasia or minimal hyperplasia noted. On removing the cystoscope, with the bladder full, suprapubic pressure is exerted to assess any flow from the urethra. Using the resectoscope with a vertical needle electrode a deep incision is made in the bladder neck at 10 o'clock. Several further cuts are made in precisely the same place until muscle fibres are clearly seen and the site of incision has opened to at least 2 cm. If an adenoma is present the incision is continued inferiorly through the adenoma. Haemostasis is secured using a ball electrode. A similar incision is made at 2 o'clock on the bladder neck. Suprapubic pressure on the full bladder with the resectoscope removed should now give a full flow of urine. A urethral catheter is placed with continuous drainage.

Results

There has been no mortality in 25 cases, although 2 patients have died subsequently (1 cerebrovascular accident and 1 myocardial infarct). Six other cases have failed to attend for follow-up. The remaining 17 patients were examined after 3 and 6 months. Follow-up excretion urography has been performed and the residual urine was reduced in all cases. Five cases had shown upper tract dilatation and all have improved (Figs. 1a, b and c).

Flow rates on 17 cases have been measured 2

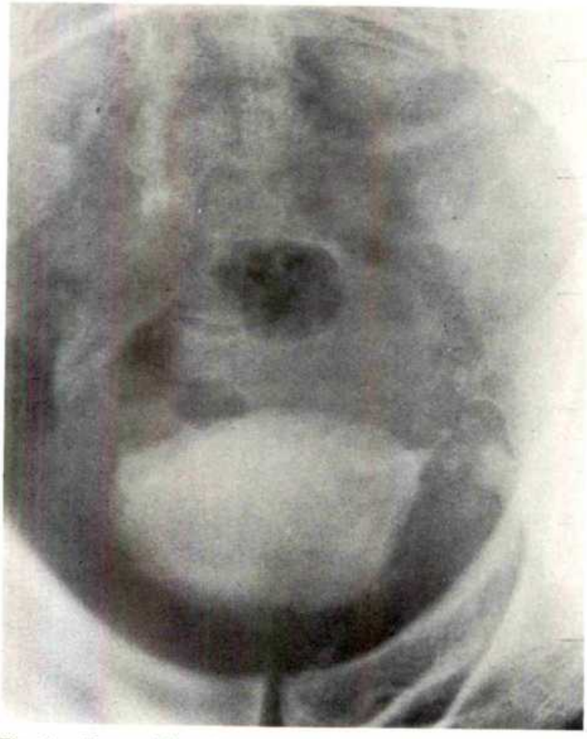

Fig. 1c Post-voiding film of same patient showing a competently emptying, thick-walled bladder after bladder neck incision. The peak flow rate was 3 ml/s.

months after operation. Eight patients had maximal flow rates of less than 5 ml/s, 4 patients had maximal flow rates between 5 and 10 ml/s and 5 patients had maximal flow rates between 15 and 25 ml/s. All voided volumes were greater than 300 ml.

Discussion

In cases of bladder outflow obstruction where the adenoma is very small or absent, transurethral resection is to be preferred to open operation. Not only is transurethral resection a quick and safe method of removing the obstruction, but open operations are much more difficult where the tissue to be removed is very small. Bladder neck incision offers a simple method of relieving outflow obstruction where the adenoma is absent or very small and the technique can be learned easily. No tissue is removed and bleeding is much reduced. Provided that the operation avoids the posterolateral prostatic branches of the inferior vesical artery, bladder neck incision very seldom causes significant haemorrhage.

The appearance of the bladder neck prior to incision is of no importance. Often the bladder neck appears wide open despite the fact that suprapubic pressure, with a full bladder, produces no flow. However, it is important to observe and ensure that the bladder neck muscle "springs open" on incision. Frequently the incision opens to such an extent that the whole of the side of the bladder neck incised is replaced by "opened" muscle and the verumontanum moves from 6 o'clock to 4 o'clock. When this happens it may not be necessary to carry out 2 incisions. Following adequate incision, or incisions, there should always be a very full flow *per urethram* on suprapubic pressure.

When a bladder neck incision is carried out in the presence of significant benign prostatic hyperplasia an adenoma, which was previously held tightly by the bladder neck and capsule, collapses into the prostatic cavity. In this circumstance further incision is not indicated and a formal transurethral resection of the adenoma should be undertaken immediately.

Bladder neck incision is not a new operation. Keitzer *et al.* (1969) incised the bladder neck in 100 patients with symptoms of outflow obstruction (not chronic retention) with a cold cutting knife. Patients were selected on grounds of age and infirmity; 75% became asymptomatic and 8% gained no benefit. Orandi (1973) reported 40 cases of transurethral incision of the prostate and bladder neck for symptoms of prostatism (not retention with overflow) and 34 were cured.

In the present series all cases followed have had symptomatic improvement. Radiological studies have shown a reduced residual urine in all cases and in the 5 cases where there was pre-operative hydronephrosis and hydroureter there has been dramatic reduction of dilatation in all cases.

Flow rate measurements have not shown a uniform improvement. Pre-operative flow rates were too low to be measured. Post-operatively only 5 cases had peak flow rates in excess of 10 ml/min. However, the 8 cases with peak flow rates of less than 5 ml/min still voided volumes greater than 300 ml and had much reduced residual urine. Presumably these low flow rates reflect the permanent atonic state of the over-stretched, decompensated bladder.

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The Effect of Pelvic Nerve Stimulation and Some Drugs on the Urethra and Bladder of the Dog

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Summary—Pelvic nerve stimulation caused an increase in pressure in both the urethra and bladder of anaesthetised dogs. The increases were only partially blocked by intravenous injection of atropine and were not significantly reduced by phentolamine, propranolol or methysergide. Quinidine produced some reduction in the bladder but not the urethral response. Hexamethonium reduced but did not abolish the responses to pelvic nerve stimulation. Close arterial injection of acetylcholine and 5-hydroxytryptamine increased the bladder and urethral pressures; noradrenaline produced a biphasic increase in urethral pressure but had no effect on the bladder; ATP increased bladder pressure but the response of the urethra was variable. The results indicate that some fibres in the pelvic nerve to the urethra as well as to the bladder are atropine resistant and suggest that transmission does not involve 5-hydroxytryptamine or noradrenaline and probably not ATP. The significance for treatment of detrusor dysfunction is discussed.

The urinary bladder and urethra are both innervated by the pelvic nerves and most, though not all, fibres synapse in the pelvic plexus. It is generally accepted that stimulation of the pelvic nerves produces contraction of the detrusor muscle resulting in an increase in bladder pressure (Elliott, 1907; Ursillo and Clark, 1956). However, the nature of the transmitter substance released from the nerves remains unsolved (Taira, 1972). The response to pelvic nerve stimulation is only partially antagonised by atropine (Langley and Anderson, 1895/96; Ambache and Zar, 1970), suggesting that all fibres may not be cholinergic. Several agents have been investigated as possible parasympathetic transmitters, including noradrenaline and adenosine triphosphate (ATP) but none have yet been confirmed (Matsumura *et al.*, 1968; Burnstock *et al.*, 1972; Alm and Elmer, 1975).

The response of the urethra to pelvic nerve stimulation has been reported as relaxation, contraction or no response (Fagge, 1902; Elliott, 1907; Graber and Tanagho, 1975). Few experiments have been done to determine the transmitters involved, although in the isolated urethra of the cat contraction was in the main atropine resistant and was unaffected by adrenergic blocking agents (Sundin and Dahlstrom, 1973).

In the present experiments the responses to pelvic nerve stimulation of the *in vivo* urethra of the dog were recorded simultaneously with those of the bladder. In an attempt to identify the transmitters involved these responses were compared with the effects of close arterial injection of postulated transmitter agents before and after administration of specific blocking agents.

Method

Adult female dogs ranging in weight from 11 to 24 kg were used in these experiments. Anaesthesia was induced by intravenous injection of nembutal (30 mg/kg body weight) and maintained with nitrous oxide supplemented with further nembutal if necessary. The systemic arterial blood pressure was monitored throughout with a cannula in the femoral artery. A cannula, through which drugs could be administered, was inserted into the femoral vein.

In order to measure the bladder and urethral pressures, 3 No. 5 ureteric catheters were introduced through the external urethral meatus (Tulloch, 1974). One (B) was pushed through to the bladder and the other 2 were placed in the proximal (U_1) and middle (U_2) thirds of the

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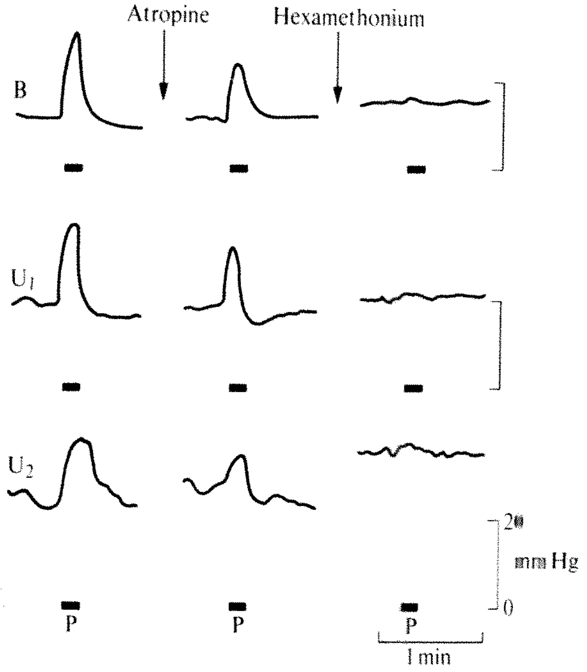

Fig. 1 The effect of atropine (0.1 mg/kg body weight) followed by hexamethonium (2.7 mg/kg body weight) on the responses of the bladder (B) and proximal (U_1) and middle (U_2) thirds of the urethra to pelvic nerve stimulation (P) in the dog. The nerve was stimulated with bipolar electrodes for 10 sec at 10 Hz and 12 V. Those responses which were not abolished by atropine were reduced by hexamethonium. In this experiment U_2 showed marked spontaneous activity and the pressure rise following hexamethonium was not a consistent reponse in other animals (Mayo *et al.*, 1974).

urethra. All 3 were connected to Statham pressure transducers (P23) and then to a Grass polygraph (7C). Each catheter was continuously perfused with normal saline at 0.1 ml/min to keep the tip open. The position of the catheters was checked when the peritoneal cavity was opened by palpating the catheters through the bladder and urethra. The catheters were taped to an Allis forceps which clasped the vaginal skin adjacent to the external urethral meatus. This maintained their position throughout the experiment.

The peritoneal cavity was opened through a mid-line incision. The pelvic nerves were identified where they lie alongside the rectum and were divided. The distal end of one nerve was placed on bipolar platinum electrodes and stimulated with trains of pulses at 10 Hz from a Grass stimulator (SD9). Supramaximal stimulation of 8 to 24 V and 1 ms pulse width was used. This current stimulated only the pelvic nerves and did not cause contraction of adjacent smooth and striated muscle. The hypogastric nerves were also divided at the level of the trifurcation of the aorta.

Agonist drugs were introduced directly into the blood supply of the urethra and bladder through a cannula tied into an internal iliac artery proximal to the urogenital branch. The artery was ligated distal to this branch. Drugs injected through this cannula included acetylcholine chloride (Hopkin and Wilkins), noradrenaline bitartrate (Winthrop), adenosine triphosphate (Sigma) and 5-hydroxytryptamine (Sigma). The blocking drugs were injected into the systemic

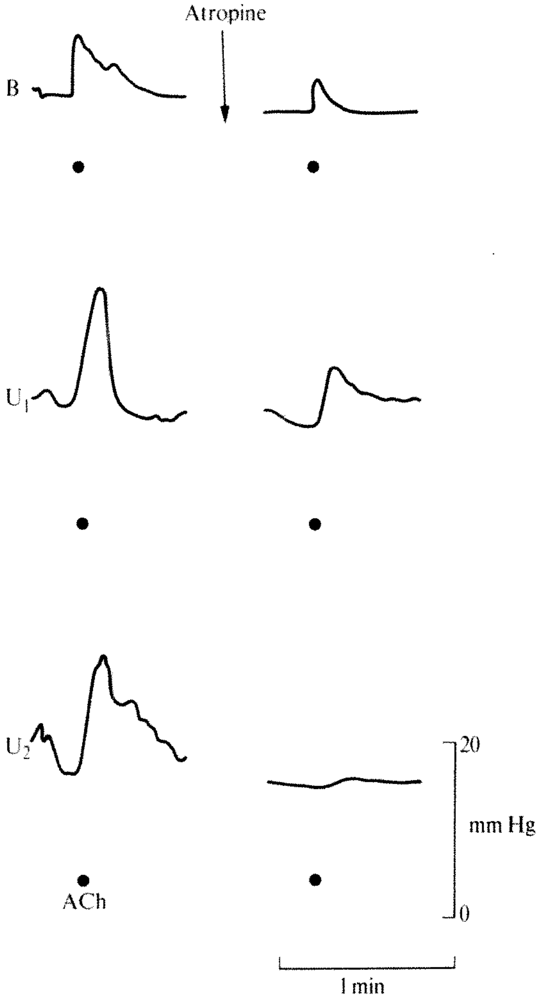

Fig. 2 The effect of atropine (0.05 mg/kg body weight) on the responses of the bladder (B) and urethra to injection of 100 μg acetylcholine (ACh) into the urogenital branch of the internal iliac artery. Larger doses of atropine abolished the responses of the bladder to ACh.

circulation via the femoral vein in order to produce a more prolonged and maintained concentration against which nerve stimulation and agonist drugs could be tested. These included atropine sulphate (Knoll), hexamethonium bromide (Sigma), quinidine gluconate (Drug Houses of Australia), phentolamine mesylate (Ciba), methysergide bimaleate (Sandoz) and propranolol hydrochloride (ICI). For each drug a separate series of experiments was performed and the doses were progressively increased until maximum effects were obtained. In some cases the combination of antagonists was investigated.

Results

The base line pressure of the bladder was usually between 3 and 11 mmHg. The bladder gradually filled during an experiment so that the volume of urine varied. However, the bladder accommodated so that the base line pressure remained constant. The pressures in the 2 parts of the urethra were often different and were always higher than in the bladder, values ranging from 7 to 23 mmHg. In some experiments both urethral pressures, but especially U_2, showed spontaneous activity.

Pelvic Nerve Stimulation

Pelvic nerve stimulation caused an increase in urethral and bladder pressures in all animals. In the bladder the increase ranged from 5 to 35 mmHg (mean ± SD = 17.4 ± 7.6; in 36 animals). In most animals 10 s was sufficient to produce a maximum response but in a few animals, particularly when the contraction was large, longer periods were necessary. Once the maximum was reached the pressure was more or less maintained throughout the period of stimulation and returned to the base line within 20 sec of the end of stimulation.

The time courses and forces of contraction, though qualitatively similar, were usually not exactly the same in the 2 parts of the urethra. The pressure increase at U_1 ranged from 6 to 39 mmHg (17.9 ± 8.7; 35 animals) and U_2 from 5 to 35 mmHg (17.7 ± 8.3; 34 animals). The response of the urethra differed from that of the bladder in that the pressure was less well maintained and often did not return immediately to the base line. In a few animals the pressure fell below the base level for a short period following the contraction.

The Effect of Cholinergic Blocking Drugs

The responses of both bladder and urethra to pelvic nerve stimulation were reduced by intravenous injection of atropine (Fig. 1). The reductions were statistically significant at the 0.1% level (Student's t test) (Table 1). The maximum inhibition occurred at a dose of 0.05 to 0.1 mg/kg body weight, increase in dose producing no further reduction. The actual reductions were variable but were never to less than 20% of the original. The greatest reduction was to 25% for B, 34% for U_1 and 20% for U_2 in one dog. These results therefore suggest that some of the fibres in the pelvic nerve supplying the urethra as well as those to the bladder are resistant to atropine.

The ganglion blocking agent, hexamethonium, (1-2 mg/kg body weight) also significantly reduced but did not abolish the responses to pelvic nerve

Table 1 The Effect of Drugs on the Pressure Increases of the Urethra and Bladder Produced in Response to Supramaximal Pelvic Nerve Stimulation at 10 Hz

	Urethra					*Bladder*				
	Control mmHg	*After antagonist mmHg*	%	*P*	n	*Control mmHg*	*After antagonist mmHg*	%	*P*	n
Atropine	22.9 ± 11.7	11.9 ± 7.8	53.8	***	18	13.7 ± 10.9	8.7 ± 8.1	63.8	***	14
Hexamethonium	19.2 ± 9.4	10.1 ± 6.8	52.8	***	17	15.3 ± 8.4	6.2 ± 4.4	40.4	***	10
Quinidine	15.5 ± 8.2	13.2 ± 6.8	85.3	NS	14	18.7 ± 8.3	13.7 ± 6.3	73.5	**	10
Phentolamine	11.2 ± 8.2	7.1 ± 3.5	63.3	NS	18	13.9 ± 8.2	9.9 ± 5.3	71.2	NS	12
Propranolol	14.4 ± 6.4	13.3 ± 6.2	92.0	NS	19	17.1 ± 7.3	17.2 ± 7.8	100.6	NS	9
Methysergide	18.9 ± 8.0	16.5 ± 6.1	87.4	NS	16	28.9 ± 7.3	20.4 ± 3.5	70.8	*	9

Measurements were taken before and after injection of the antagonist drug into the femoral vein and the results compared using the Student's t test. No other antagonist drugs had previously been given. Probability (*P*) *** = <0.1%, ** = <1%, * = <5%, NS = not significant. Values shown are mean ±SD. n = number of observations.

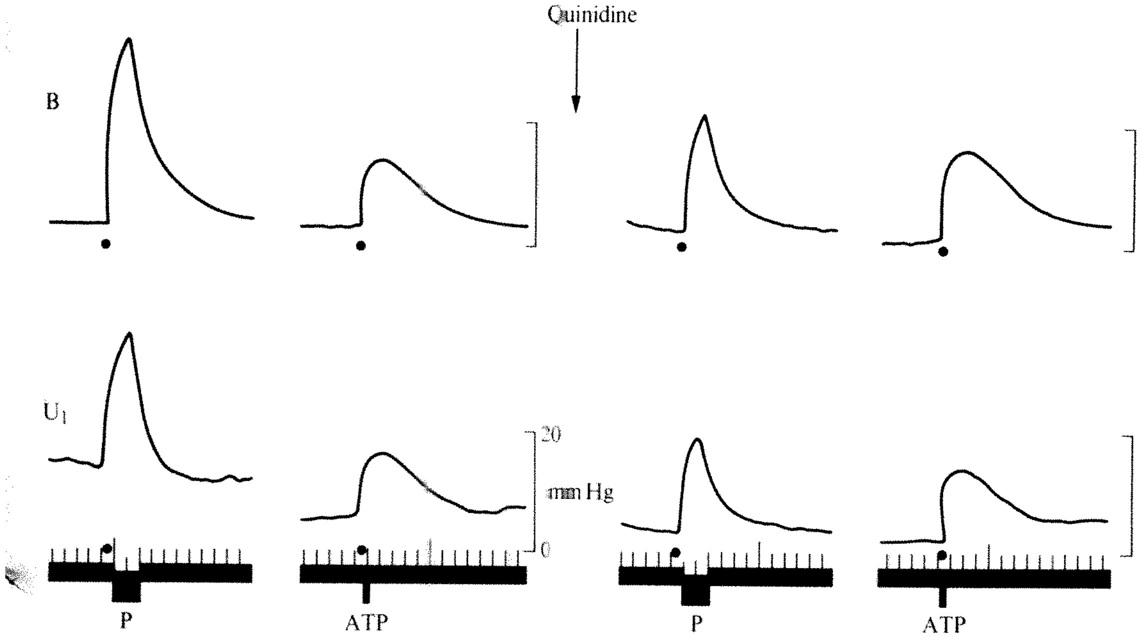

Fig. 3 The pressure responses of the bladder and urethra to pelvic nerve stimulation (P) (20 V) and to close arterial injection of ATP (3 mg). Injection of quinidine at 8.6 mg/kg body weight into the femoral vein slightly reduced the nerve responses but did not block the action of ATP. The time marker is 5 s.

stimulation (Table 1). It had less effect on the urethral contraction, suggesting that relatively more fibres in the pelvic nerve pass directly to the smooth muscle of the urethra without synapsing in the pelvic plexus. In the presence of both atropine and hexamethonium on average about 25% of the urethral response remained, whereas in the bladder less than 10% was present and in some animals the responses of both urethra and bladder were completely abolished (Fig. 1). The residual responses were not affected by gallamine and are presumably produced by non-cholinergic fibres that do not synapse in the pelvic plexus peripheral to the point of stimulation.

The Action of Some Drugs

(1) *Acetylcholine* By injection of acetylcholine (50-150 μg) into the arterial supply to the urethra and bladder, responses approaching maximum could be obtained with only minor changes in systemic blood pressure. The responses of both the urethra and the bladder were always an increase in pressure (Fig. 2). The maximum responses were usually less than those produced by pelvic nerve stimulation (urethra 3-19 mmHg: 53% of pelvic response in 14 animals; bladder 2-19 mmHg; 66%). The time courses of both onset and decay of the contractions were longer than the nerve mediated responses, and there was

Table 2 The Effect of Antagonists, Injected into the Femoral Vein, on Responses to Close Arterial Injection of Agonist Drugs

		Urethra					*Bladder*				
Agonist	*Antag.*	*Control mmHg*	*After antagonist mmHg*	*%*	*P*	n	*Control mmHg*	*After antagonist mmHg*	*%*	*P*	n
ACh	Atr	12.2±7.7	2.8±4.1	22.9	***	14	6.0±3.4	0.7±1.6	11.1	**	7
ACh	Hex	11.6±2.8	8.0±2.8	69.2	*	8	10.9±5.3	8.2±3.2	75.9	NS	6
ATP	Q	3.8±3.3	5.25±4.1	138.2	NS	10	5.4±3.5	5.3±3.9	98.1	NS	5
N Adr	Phent	8.4±6.8	−0.9±1.7	<0%	***	13	1.4±0.9	0.1±0.3	9.1	NS	8
5HT	Meth	6.2±9.1	3.0±9.9	48.3	NS	12	13.1±3.5	6.8±5.9	51.9	*	7

Details as in Table 1.

no evidence of relaxation of the urethra below the base level following the contraction. The pressure increase in the urethra did not follow exactly that of the bladder, suggesting that they were contracting independently.

Intravenous injection of atropine (0.05-0.1 mg/kg body weight) reduced but did not abolish the response of the urethra to acetylcholine but effectively abolished the bladder response (Table 2). Hexamethonium (1-2 mg/kg body weight) had little effect on responses of either the urethra or bladder and did not further reduce the responses of the urethra that remained after atropine. This therefore suggests that injected acetylcholine has its major action directly on the smooth muscle and little effect on the ganglia. It also indicates that the atropine resistant response of the urethra is not due to a nicotinic action of acetylcholine which would be blocked by hexamethonium. Intravenous administration of gallamine (6 mg/kg body weight) also failed to produce a reduction.

(2) *Adenosine triphosphate (ATP)* It has been suggested that the atropine resistant excitation of the bladder may be due to the release of the purine nucleotide ATP and that this is specifically blocked by quinidine (Burnstock *et al.*, 1972). The effects of quinidine on the responses to pelvic nerve stimulation and close arterial injection of ATP were therefore investigated. ATP (3-6 mg) always produced an increase in bladder pressure which was up to half that produced by pelvic nerve stimulation (0.5-15 mmHg; mean 27%; in 10 animals). The response of the urethra was variable, depending on dose and base tone. At low doses there was normally a decrease in pressure; at high doses, however, the pressure recorded closely followed that of the bladder, probably because contraction of the bladder pulled open the bladder neck. When the urethral tone was high the pressure initially dropped to the bladder pressure before rising in parallel.

Quinidine, administered through the femoral vein at doses of 7 to 13 mg/kg body weight, caused some reduction in bladder and urethral responses to pelvic nerve stimulation (Fig. 3). The reduction in the urethral response was statistically not significant but the bladder reduction was possibly significant (Table 1). Quinidine produced no change in responses to acetylcholine and did not block the contractile response of the bladder to ATP (Table 2), although the inhibitory response was no longer seen. ATP did not act by causing the release of acetylcholine since atropine was without effect on the response to ATP.

(3) *Biogenic amines* Close arterial injection of noradrenaline (10 μg) usually had no effect on bladder pressure but produced a biphasic change in urethral pressure (Fig. 4). A contraction also occurred in response to the α-agonist phenylephrine whereas the later relaxation was mimicked by the β-agonist isoprenaline. The pressure responses of noradrenaline and phenylephrine were abolished by phentolamine (0.5-1.0 mg/kg body weight) (Table 2). This α-blocking drug also produced a slight reduction in the responses to pelvic nerve stimulation of both the bladder and urethra (Fig. 5) but this was not statistically significant (Table 1). Phentolamine could have a non-specific action since there was also some reduction in the responses to close arterial injection of acetylcholine. The β-blocking agent propranolol (0.1-0.3 mg/kg body weight) was without effect on the responses to pelvic nerve stimulation (Table 1).

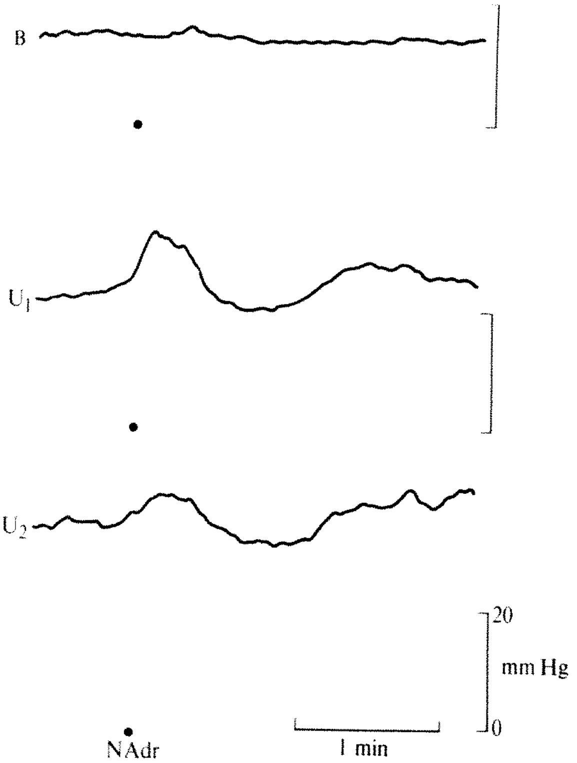

Fig. 4 Close arterial injection of 10 μg noradrenaline (N Adr) produced almost no pressure change in the bladder (B) and a biphasic response in the urethra.

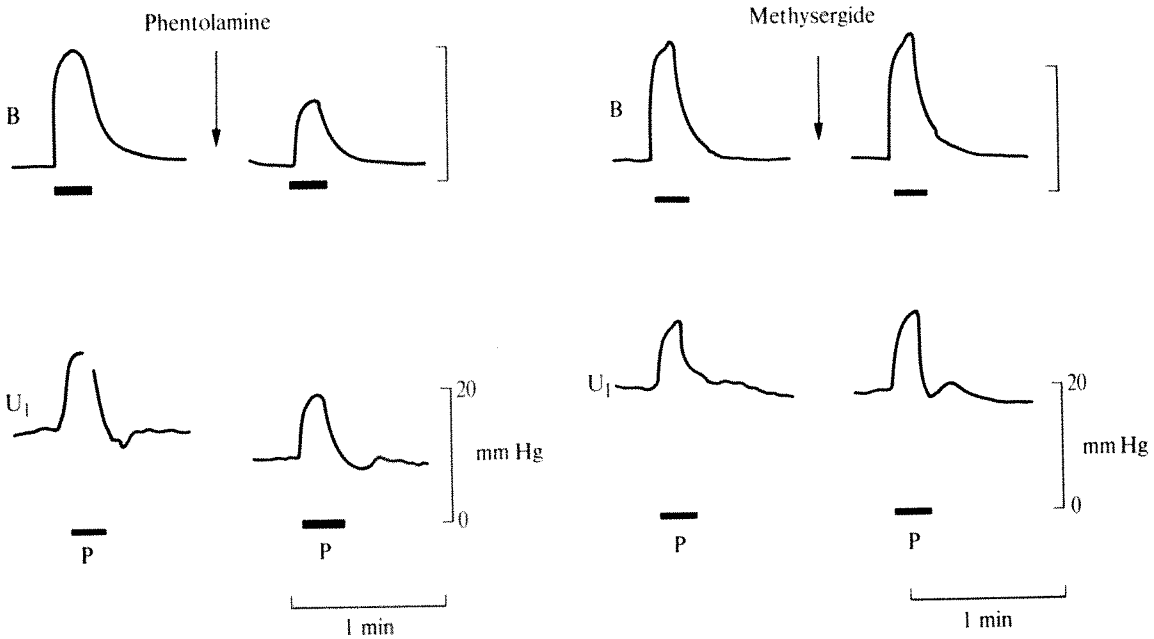

Fig. 5 The effects of methysergide (0.1 mg/kg body weight) and phentolamine (0.9 mg/kg body weight) on the responses in 2 dogs to pelvic nerve stimulation (P) (10 and 12 V).

5-hydroxytryptamine (5HT) has been shown to produce a powerful contraction of the isolated bladder (Matsumura *et al.*, 1968) and was therefore investigated in the anaesthetised dog. Close arterial injection of 5HT (20-50 μg) caused an increase in bladder pressure of 6.5 to 22 mmHg (34-90% of the response to nerve stimulation in 9 animals). The response of the urethra was also predominantly an increase in pressure, though this was often complex, with 2 or more steps which were sometimes preceded or separated by a decrease in pressure (Fig. 6). The initial contraction usually closely followed the increase in bladder pressure. When the urethral pressure was already high, this often dropped towards the bladder pressure but the activity of the urethra continued after the bladder pressure had returned to its original level. Methysergide (0.04-0.1 mg/kg body weight) slightly reduced the responses of both the bladder and urethra to pelvic nerve stimulation (Fig. 5) (Table 1) but failed to abolish the response to 5HT (Fig. 6) at this or higher concentrations (Table 2). Since the action of 5HT was greatly reduced by phentolamine (0.5-1.0 mg/kg body weight) (Fig. 6) it may produce its effects by action on α-adrenergic receptors.

Discussion

In the present experiments the responses of the bladder and urethra of the dog to electrical stimulation of the pelvic nerves were investigated. The responses recorded were not due to reflex activity involving the micturition centre in the sacral cord or of the higher centres since both pelvic and hypogastric nerves were divided. Athough the pudendal nerves were not divided, none of the reflexes as described by Barrington (1941) had both afferent and efferent pathways in the pudendal nerves (Garry *et al.*, 1959). The observed pressure changes were therefore direct responses to nerve stimulation and not secondary effects from Barrington's reflexes. The introduction of agonist drugs into the urogenital branch of the internal iliac artery allowed high concentrations to be obtained in the bladder and urethra so that direct responses were again recorded with minimal central cardiovascular effects.

The results obtained confirm earlier findings that the bladder responses to pelvic nerve stimulation are partially resistant to atropine. They also indicate that in the urethra, too, the responses are not completely blocked by atropine. The atropine resistance of the bladder has been

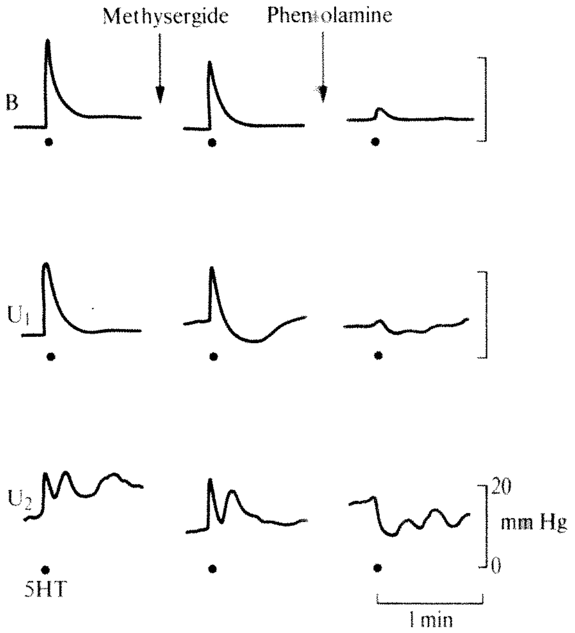

Fig. 6 The responses to close arterial injection of 5HT (30 μg) were little affected by methysergide (0.1 mg/kg body weight) but were greatly reduced by phentolamine (0.7 mg/kg body weight).

explained by the inaccessibility of the cholinergic receptors (Ursillo and Clark, 1956) or by the high local concentration of acetylcholine released by the nerves (Hukovic *et al.*, 1965). More recently it has been suggested that some of the fibres in the pelvic nerve are non-cholinergic and Burnstock *et al.* (1972) called these fibres "purinergic", believing that the transmitter involved may be the purine nucleotide, ATP. These workers used quinidine to block, in parallel, the responses of strips of guinea pig bladder to ATP and field stimulation. In the present experiments ATP caused some increase in bladder pressure and the urethral response was variable. However, quinidine failed to block these and was probably without effect on the responses to pelvic nerve stimulation. The view that ATP is the transmitter cannot be excluded but the results do not support the conclusion that quinidine is a specific antagonist.

It has been suggested that some of the postganglionic fibres in the pelvic nerve of the rat are adrenergic (Alm and Elmer, 1975). However, in the dog neither phentolamine nor propranolol significantly reduced the urethral or bladder responses. Close arterial injection of the adrenergic transmitter, noradrenaline, failed to increase the bladder pressure but produced a biphasic response in the urethra, the initial contraction phase of which was blocked by phentolamine, suggesting that α-receptors also occur in the bladder. It is possible that local vasoconstriction prevented the injected noradrenaline reaching the bladder. The lack of effect of phentolamine or methysergide on the response to pelvic nerve stimulation suggests that neither noradrenaline nor 5-hydroxytryptamine is involved in transmission.

This experimental work highlights the complexity of possible transmitters involved in the physiology of micturition and may suggest different experimental approaches to the treatment of bladder dysfunction. Turner-Warwick (1975) has pointed out the difficulties that urologists have in controlling with drugs the symptoms of patients with detrusor instability. Anticholinergic drugs such as propantheline bromide act only on the cholinergic nerves and in the dog at least only about 40% of responses to pelvic nerve stimulation are blocked by muscarinic anticholinergic drugs. In detrusor instability it may be the non-cholinergic nerves which are excessively active. Better results might be expected if the drug therapy were aimed at ganglion blockade of the pelvic plexus with, for example, hexamethonium, but the dose would have to be limited because of the cardiovascular effects. Effective ganglion blockade would block those nerves that synapse in the pelvic plexus, which, as the present experiments suggest, include some non-cholinergic fibres. Further work must be carried out to identify the transmitters released by these nerves to the bladder and urethra and their specific antagonists. The present experiments suggest that it is unlikely that quinidine, phentolamine or methysergide can be of value for the treatment of bladder dysfunction.

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The Effect on the Bladder Pressure of Sudden Entry of Fluid into the Posterior Urethra

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Summary—The posterior urethra was stimulated by the rapid injection of saline against the urethral wall. The effect was studied in 50 female patients attending a urodynamic clinic. The injection was made via a double lumen catheter, and bladder, urethral and rectal pressures were observed during and after the ingress of fluid.

The results indicate that sudden entry of fluid into the posterior urethra does not initiate a detrusor contraction even in those patients in whom the injection of fluid is painful.

The relevance of these results in relation to the unstable bladder and urodynamic tests is discussed.

The entry of fluid into the urethra may initiate a bladder contraction. This possibility has been the subject of controversy for over a century. In order to understand more clearly the physiology of micturition and the results of urodynamic tests, it would be valuable to know whether bladder contractions can be provoked in this way.

In the healthy adult, urine enters the urethra only during micturition. However, fluid may be present in the urethra in other circumstances as, for example, in patients with urinary incontinence and during some diagnostic procedures such as measurement of urethral closure pressure profile.

In genuine stress incontinence* urine enters the urethra following rises in intra-abdominal pressure and there is no change in intrinsic bladder pressure, whereas in the unstable bladder a detrusor contraction may follow and this may cause the bladder neck to open. The stimulus for this reaction has not been clearly identified, but one theory is that the detrusor contracts because the rise in intra-abdominal pressure stimulates stretch-receptors in the bladder wall or visceral peritoneum. Where there is both an unstable bladder and a mechanically incompetent bladder neck the entry of fluid into the urethra could itself act as a stimulus to potentiate or even initiate the detrusor activity.

Fluid is infused into the posterior urethra in some methods of measuring the urethral pressure profile. If reflex bladder contractions can be caused by this infusion then the test results will be distorted.

In this study we have attempted to test the hypothesis that fluid entering the posterior urethra causes a reflex contraction of the bladder.

Patients and Method

The study was conducted on 50 consecutive female patients, aged between 25 and 79 years (mean 51 years), who had been referred for urodynamic evaluation of their symptoms prior to treatment.

Investigation on this unit includes continuous medium-fill cystometry, using normal saline at 37°C instilled at a rate of 50 ml per min with the patient supine. In each patient an attempt is made to provoke detrusor contractions by asking her to cough whilst standing up with a full bladder. Detrusor instability is diagnosed if there are any transient changes in intrinsic bladder pressure during these procedures. Urethral pressure profiles are measured by the method des-

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* In this paper all methods, definitions, and units conform to the standards proposed by the International Continence Society (1976) except where specifically noted.

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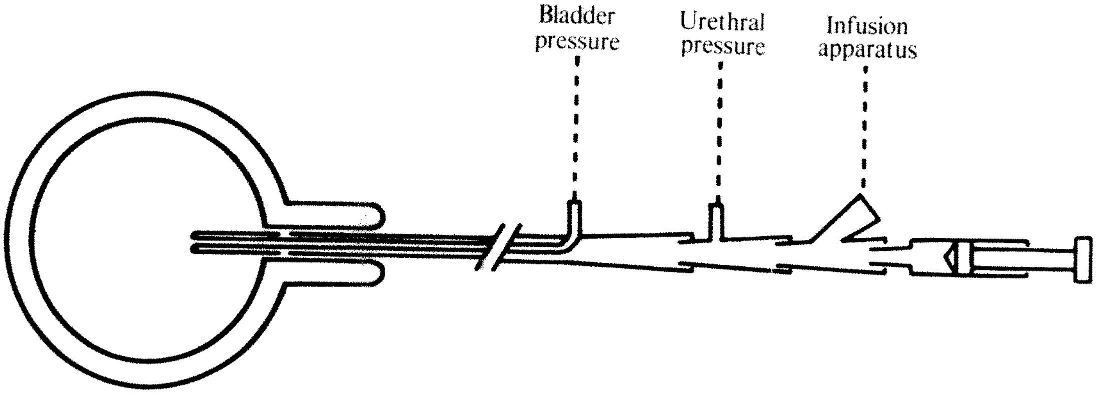

Fig. 1 Diagram showing the arrangement of the catheter, syringe and pressure lines.

cribed by Brown and Wickham (1969), in order to identify those patients with urethras of short functional length or low maximum closure pressure.

Forty-two of the 50 patients suffered from urinary incontinence. The other 8 were being investigated for other reasons. Two had had recent incontinence surgery and were being assessed objectively in the post-operative period. One had an atonic bladder secondary to diabetic neuropathy. The remaining 5 had symptoms of increased frequency of micturition, urgency and nocturia.

As part of their general investigation, supine cystometry was performed first using a double lumen bladder/urethral catheter*. When the patient was uncomfortably full, the infusion rate was reduced to 2 ml per min so that the urethral pressure could be measured via the side holes in the catheter.

The catheter was withdrawn to a point 1 cm from the bladder neck (as defined on the urethral profile), and the infusion stopped. With the catheter connected as shown, 1 ml of normal saline at 37°C was then injected against the urethral wall (Fig. 1). The injection lasted only a fraction of a second. During the injection and for approximately 10 sec afterwards, intravesical, urethral, and rectal pressures were observed.

The same procedure was repeated later when the volume of fluid in the bladder had been reduced to 150 ml.

In those patients who demonstrated detrusor contractions during supine cystometry the saline was injected at a time when the bladder was not contracting.

Results

In none of the cases investigated was there any change in intrinsic bladder pressure following the injection. This was true even in patients with grossly unstable bladders in whom detrusor contractions had been provoked by medium-fill cystometry alone.

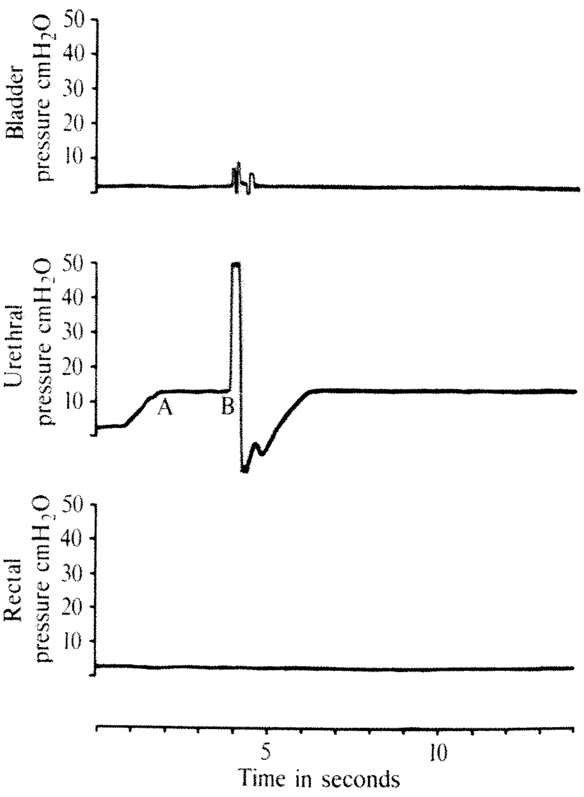

Fig. 2 Bladder, urethral and rectal pressures during and after the injection of 1 ml saline into the proximal urethra. (A: finding the bladder neck; B: the injection of saline).

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* Portex Ltd, Hythe, Kent, England.

Table 1 Classification of Patients According to Final Diagnosis, with the Sensation to Injection Tabled Alongside

Diagnosis	*No.*	*Sensation*		
		Nil	*Slight*	*Pain*
Genuine stress incontinence (G.S.I.)	16	2	11	3
Unstable bladder (U.B.)	14	2	10	2
Mixed (G.S.I. and U.B.)	7	–	5	2
Other	13	3	5	5

The form of the readings is shown in Figure 2. The high urethral pressure recorded during the injection is due to the relative positions of the syringe and pressure measuring line. The recorded bladder pressure is also disturbed during the injection because of the concentric arrangement of the catheter lumina.

Forty-three patients reported feeling the injection, but most of them (31 patients) described it as a slight "pricking sensation" or a "pins and needles" feeling. The sensation was the same when the bladder was full to capacity as when its volume had been reduced to 150 ml.

In Table 1 sensation is shown alongside the diagnosis. It can be seen that there is no obvious relationship between them.

The 13 patients in the group entitled "Other" include the 8 continent patients described above, and 5 others in whom pressure studies were normal. Subsequent investigation in 9 of these 13 suggested that these were suffering from recurrent cystitis or urethritis. In 1 the only abnormality detected was a small capacity bladder.

Twelve patients considered the injection to be painful, and in 6 of these it was very painful. In these 6 the test was performed only once because of the discomfort it caused.

We thought that there might have been a link between the pain experienced and a diagnosis of urethritis. However, though 7 patients who did register pain were shown on subsequent endoscopic examination to have urethritis, 5 others were not. Also 3 patients were later shown by endoscopy to have urethritis, yet saline injection had not caused pain. There appeared therefore to be no obvious diagnostic significance to the painful sensation experienced by some patients.

Discussion

During voiding in the normal female it is usual for urethral pressure to fall several seconds before the onset of detrusor action (Tanagho *et al.*, 1966). According to Muellner (1949, 1951) it is the relaxation of the pelvic floor itself and the downward tug on the bladder neck which sets off detrusor reflexes. Others suggest that it is the distortion of the trigone and the bladder base (Tanagho *et al.*, 1966).

Many attempts have been made to identify the neurological pathways involved, in both the laboratory animal and the human (Barrington, 1921, 1931; White and Smithwick, 1942; Nathan and Smith, 1951; Garry *et al.*, 1959; Mahony *et al.*, 1977). Barrington described 7 micturition reflexes in the cat. In 3 of these running water through the urethra or distension of the proximal urethra caused contraction of the detrusor (Barrington's second, third and seventh reflexes). More recently, Mahony *et al.* (1977) have described 12 reflexes, some facilitative and some inhibitory. In 3 of these, urine flow across the urethral mucosa is said to cause continued detrusor contraction.

Whilst there appears to be no doubt that posterior urethral reflexes facilitate the continued contraction of the detrusor once it has started, their role in the initiation of micturition is not clearly understood.

Goltz (1874) suggested that the expression of drops of urine into the posterior urethra caused the micturition reflex and also a desire to micturate. His deductions were made from studies on the spinal animal, but neither Guyon (1887) nor Denny-Brown and Robertson (1933) were able to demonstrate any such facilitative reflexes in the human. Karlson (1953), on the other hand, described definite detrusor contractions when fluid was introduced into the proximal part of the human female urethra, whether the bladder was empty or full. Angell (1969) also believed that fluid entering the posterior urethra could trigger off detrusor contractions.

In the last decade the investigation of urinary incontinence using refined urodynamic techniques has become popular. Though much information can be gained from transurethral measurement of intravesical and intraurethral pressure, there still lingers a suspicion that irritation of the posterior urethral mucosa by a catheter or fluid is a source of error in these diagnostic procedures. Withdrawal of a urethral catheter is said to cause detrusor contraction in the unstable bladder (Turner-Warwick, 1976) and detrusor contractions have been recorded during urethral closure pressure profile measurement in patients with uninhibited bladder (Torrens, 1977).

The unstable bladder described by Bates *et al.* (1970) and Bates (1971) is a bladder which can be provoked into activity by rapid filling, erect filling and stress situations such as coughing whilst the patient is standing up. It has been suggested that these manoeuvres cause extra stimulation of receptors in the bladder wall or visceral peritoneum, which in turn causes detrusor contraction. If, however, they caused a small amount of fluid to be forced into the posterior urethra and this fluid initiated a micturition reflex, then our view of detrusor dyssynergia incontinence might be quite different.

In 1976 Beck *et al.* reported satisfactory surgical results in patients with demonstrable unstable detrusors and bladder neck funnelling. They postulated that this funnelling had been the cause of the detrusor activity. Warrell (1976) also thought that on some occasions at least the presence of urine in a mechanically weak sphincter seemed to irritate the bladder.

We had hoped that our study might provide an additional provocative test whereby patients with unstable bladder could be subdivided into 2 groups, one of which would be suitable for surgical repair of the bladder neck. In practice it did not do so.

Our results indicate that whatever the type of urinary incontinence in the female, entry of fluid into the posterior urethra does not cause any detrusor activity. The bladder remains stable even though a considerable volume (for the posterior urethra) is injected into it very quickly.

It would seem that the concept of fluid in the posterior urethra initiating the micturition reflex is either unfounded or not important when assessing patients for treatment.

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One-stage Excision Urethroplasty for Stricture

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Summary—Forty-two patients have had a one-stage excision urethroplasty for localised strictures in the bulbous urethra. The stricture recurred in 2 patients, one requiring a scrotal flap urethroplasty and the other a further excision and repair with a good result.

With careful selection this operation gives very good results and has been used successfully in the primary repair of complete rupture of the bulbous urethra.

Excision of urethral strictures and primary repair by end-to-end anastomosis were described in the early nineteenth century but the results were unsatisfactory. Heusner (1883) carried out excision and suture and Guyon (1892) excised the stricture incompletely, leaving an intact strip on the posterior urethral wall. Rochet (1899) advocated urinary diversion and claimed increased success. Russell (1915) excised the stricture and only partially repaired the urethra. He established the principle of the buried strip which was later successfully applied by Browne (1949) to hypospadias repair, and by Johannson (1953) to the problem of urethral stricture. Marion (1912) used a midline perineal approach for stricture and acute trauma of the bulb. He excised the diseased or damaged tissue and repaired the urethra by direct end-to-end anastomosis.

At present, one-stage excision and repair are not popular and Blandy (1976) stated that only 1 in his series of 210 urethroplasties was treated by this method. Eight had been treated by one-stage excision and repair elsewhere and all of these required revision.

In contrast with the depressing results which have generally been recorded, ours have been encouraging.

Patients

Forty-two patients aged from 20 to 50 years were reviewed. The stricture was bulbar in 41 and penile in 1 patient. One patient had 2 strictures that were 5 cm apart.

The usual criteria for the failure of conservative management were applied. The one-stage excision and repair were strictly reserved for cases of non-inflammatory origin not suitable for internal urethrotomy and in which scarring and damage to the mucosal lining were localised to a short segment. The stricture was usually single and was distal to the external sphincter. A detailed history and a urethrogram of good quality enabled the surgeon to determine whether a case was suitable, but the final decision was made when the stricture had been exposed; if the scarring and diseased mucosa extended for more than 1 cm either side of the stricture, excision of the stricture was not performed.

The aetiology was trauma in 17 patients, inflammation in 6, following transurethral resection in 8 and after catheterisation in 2. Three patients were thought to have congenital strictures and in 6 the cause was not known.

Operative Technique

Principles

Not only must the stricture be excised, but all gross peri-urethral scar must be removed; otherwise a recurrence will probably occur. The cut ends of the urethra, which is divided completely, must reveal healthy mucosa and a normal calibre urethra. It is essential to mobilise the distal urethra so that a tension-free anastomosis can be fashioned and first intention healing ensured. In order to avoid a circumferential scar (which may lead to a recurrence), a zig-zag (Sheffield) or oblique (Oxford) suture line is designed. As the repair cannot be fully water-tight the urine is diverted so that fistula formation and excessive peri-urethral scarring will be avoided. In the

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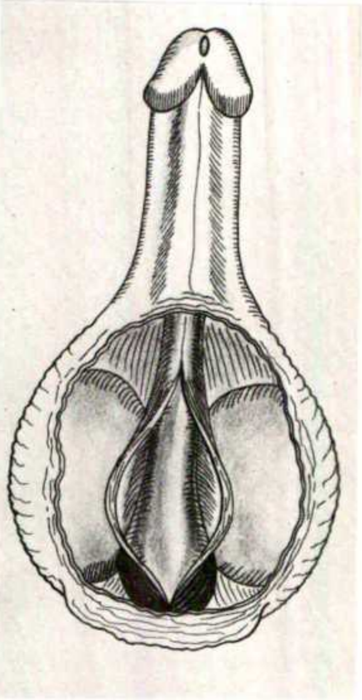

Fig. 1 Exposure of the urethra showing reflection of the bulbo-spongiosus muscle.

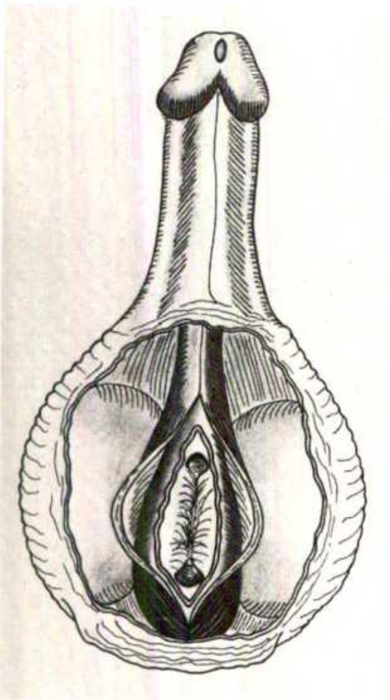

Fig. 2 The stricture opened.

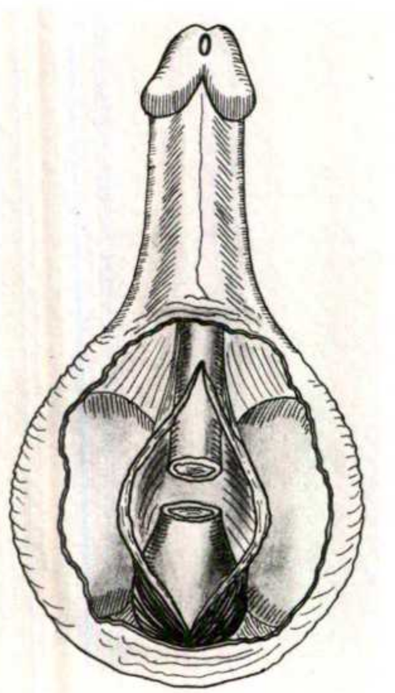

Fig. 3 After excision of the stricture.

Oxford series a suprapubic cystotomy was used, but in Sheffield an indwelling catheter was relied upon. In both centres 3/0 Dexon was used for suturing.

The Operation

Under general anaesthesia, with the patient in the exaggerated lithotomy position, a metal sound of large calibre is passed as far as the stricture. A midline perineal incision 4 to 5 cm long is made with the stricture site (as determined by the position of the tip of the sound and the urethrogram) in the centre. The bulbo-spongiosus muscle is divided in the midline, freed from the sheath of the corpus spongiosum which invests the urethra, and held in the blades of a Turner-Warwick self-retaining retractor (Fig. 1). The urethra with its surrounding corpus spongiosum is freed above and below the stricture from the underlying sheath of the corpus cavernosum for a distance of 3 to 4 cm distally and 1 to 2 cm proximally. Only when this has been accomplished and haemostasis secured is the urethra opened in the midline by cutting on to the sound just distal to the stricture for a distance of about 1 cm. Stay sutures are inserted to reveal the urethral lumen and the face of the stricture (Fig. 2). A probe is passed through the stricture and the incision is continued in the midline, dividing the stricture and entering the urethra proximal to the stricture. If the channel is lost in the scar tissue, the careful application of suprapubic pressure may be followed by the escape of urine from the proximal end of the strictured urethra which acts as a guide. Only rarely is it necessary to have to pass a sound from the bladder into the posterior urethra so that it can be located. It is important to examine the lining mucosa to be certain that the urethra and not a false passage is being followed. The latter has a reddish coloured lining and the passage of an instrument along it is resisted through its whole length. Having opened the proximal urethra it should now be possible to pass a wide-bore sound with ease. If the stricture is localised and the urethra on either side appears healthy the stricture is excised, leaving a gap which should not exceed 2 cm (Fig. 3). If necessary it is now easy to free the distal urethra further by dividing its attachments to the sheath of the corpus cavernosum in the midline.

Each cut end of the urethra is cut obliquely or incised in 2 places opposite to each other to

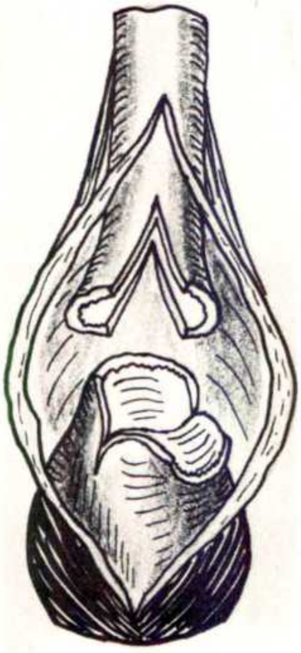

Fig. 4 The urethral flaps.

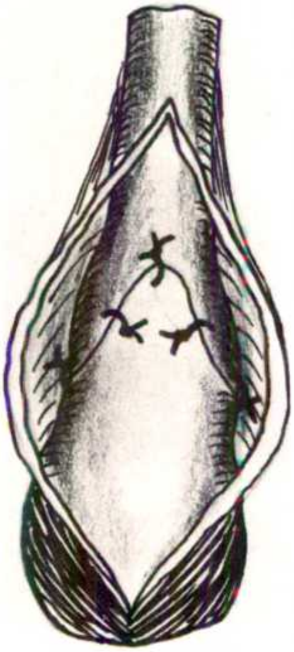

Fig. 5 The flaps sutured into position.

fashion 4 flaps which will be interdigitated. The proximal end (mucosa and corpus spongiosum) is incised at 3 o'clock and 9 o'clock and the distal end at 12 o'clock and 6 o'clock (Fig. 4). Closure is made with 3/0 Dexon (Fig. 5). The sutures are first inserted posteriorly and left long until about 4 are in position. They are tied and a catheter inserted before final urethral closure is carried out. Tension on the suture line can be relaxed by suturing the distal urethra to the corpus cavernosum sheath.

The repair is covered by re-uniting the 2 halves of the bulbo-spongiosus muscle. If haemostasis is secured, the midline skin incision is closed in 2 layers and covered by an occlusive dressing. In the Oxford series a suprapubic cystotomy was performed and a Redivac drain put alongside the anastomosis for 48 h.

If it is decided that a one-stage repair is not feasible the midline exposure is still valuable. A viable scrotal flap can still be raised and the midline incision used to obtain access to the urethra, particularly when the scrotal flap is sutured into place.

Post-operative Care

In the Oxford series a descending cystourethrogram was performed a week post-operatively. If the radiograph was satisfactory, with no extravasation, the suprapubic catheter was clamped and later removed.

In Sheffield the urethral catheter was removed between the seventh and tenth days, when a micturating cystourethrogram was performed. It was not considered necessary or desirable to pass sounds post-operatively in either series.

Results

All patients have been studied post-operatively with an ascending urethrogram and followed up for 3 months to 6 years (Figs. 6 and 7).

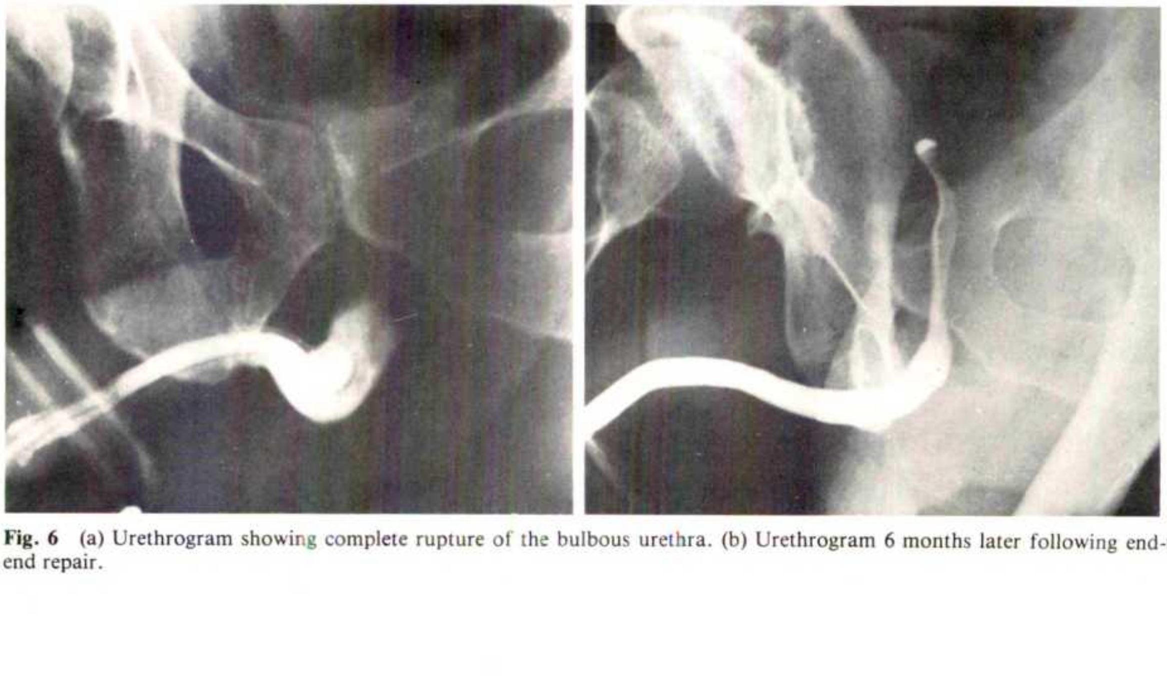

Fig. 6 (a) Urethrogram showing complete rupture of the bulbous urethra. (b) Urethrogram 6 months later following end-to-end repair.

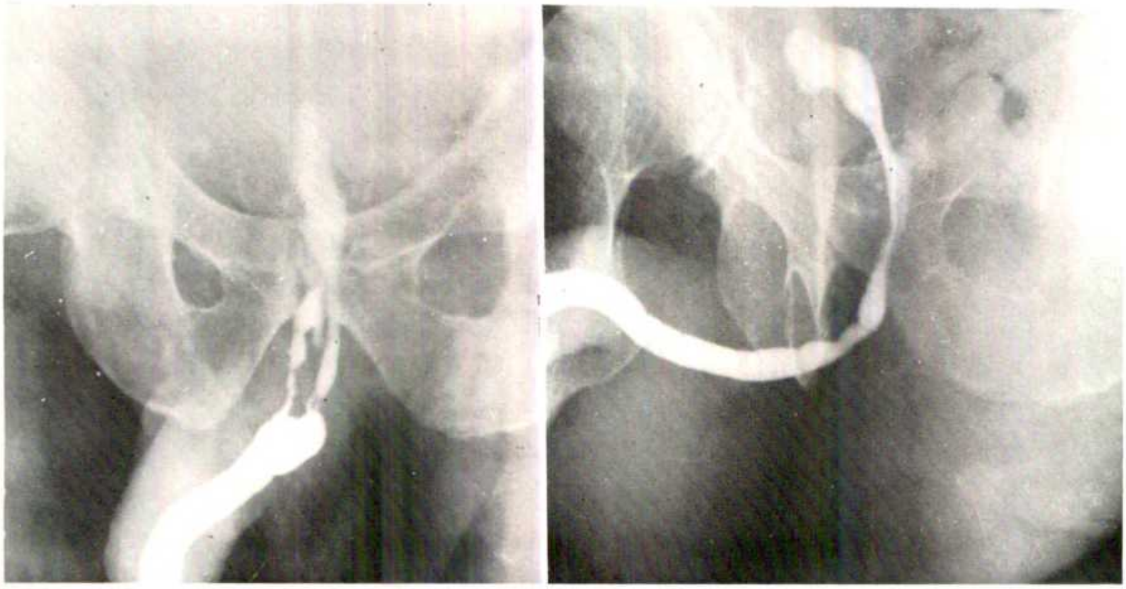

Fig. 7 Urethrograms (a) before and (b) after excision and end-to-end repair in a patient with a false passage.

Only 2 patients have had a recurrence of a bulbous stricture: the first followed an infection and abscess formation and he later had a two-stage scrotal flap urethroplasty; the second had a further end-to-end repair with a successful result.

Two patients, who had had a recurrence following a previous end-to-end repair at another centre, both had a successful re-operation with primary suture.

In the patient who had 2 strictures 5 cm apart, each was excised separately and primary repair performed.

Three patients who had a primary suture for acute rupture of the bulbous urethra within 24 h of injury have all had excellent results.

The majority of the urethrograms show remarkably good urethral calibre. In a few some narrowing is shown but dilatation has not been necessary and these patients pass a good stream. One patient has attacks of urinary infection requiring antibiotic therapy.

Discussion

The good results of this series of excision and primary end-to-end anastomosis for urethral stricture are almost certainly due to the very careful selection of cases.

This operation has the advantage of a one-stage procedure and does not introduce scrotal skin with its sometimes attendant problems of hair formation.

Internal urethrotomy has recently become more popular and a number of our patients may well have been suitable for this procedure. The selection of cases and the results of this operation have yet to be assessed and compared with primary excision.

Acknowledgement

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Can Follicle Stimulating Hormone Estimation Replace Testicular Biopsy in the Diagnosis of Obstructive Azoospermia?

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Summary—Sixty azoospermic men were investigated by means of testicular biopsy and estimation of serum follicle stimulating hormone (FSH) levels. High FSH levels when associated with small testes indicated severe testicular damage. We suggest that these findings offer sufficient evidence to regard such patients as infertile and that further investigation is unnecessary. In men with normal FSH levels testicular biopsy is still necessary for accurate diagnosis; in practice this may often be done at the same time as epididymovasostomy.

Azoospermia is caused either by an obstructive lesion in the seminiferous tract or by spermatogenic failure due to a variety of causes. Testicular biopsy is a commonly used method of differentiating the 2 types of azoospermia but is an invasive technique with potential complications. Severe maturation arrest relates closely to the finding of reduced testicular size and also results in an elevation of the level of follicle stimulating hormone (Pryor *et al.*, 1976). This study was undertaken to evaluate the usefulness of serum follicle stimulating hormone levels to predict those azoospermic men with severe maturation arrest and thus to enable testicular biopsy to be avoided in these cases.

Patients and Methods

Sixty azoospermic men were studied. They had attended the infertility clinics at the Western Infirmary, Glasgow and the Middlesex Hospital, London and were found to be azoospermic on 2 successive seminal examinations. A full physical examination was carried out and blood was taken for the estimation of serum FSH. The serum from the Glasgow patients was stored at −4°C and transported on ice to the Institute of Nuclear Medicine at the Middlesex Hospital, where all FSH estimations were performed. The laboratory range of FSH levels in the serum for normal men is 2.5 ± 2.5 u/l.

Testicular biopsy was performed under general anaesthesia. If only 1 testis was reduced in size the biopsy was taken from the larger testis. The biopsy specimens were fixed immediately in either Bouin's or Davidson's fluid. At the same time, testicular tissue was taken for meiotic analysis. Analysis of mitotic chromosomes was made from a blood sample taken at the time of biopsy.

Results

There were no operative or anaesthetic complications of testicular biopsy in this series.

Table 1 Pathology in 30 Men With Abnormal Biopsy

17 Sertoli cells only	13 del Castillo 2 Klinefelters 1 45X 46XY 1 46X	Absent meiosis
3 maturation arrest	2 primary spermatocyte stage (arrested in prophase) 1 spermatid stage	
4 post-inflammatory scarring 1 focal tubular atrophy 4 depressed spermatogenesis 1 non-specific orchitis	In all of these cases spermatogenesis was proceeding to completion in some areas in the biopsy and meiotic analysis was normal	

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Table 2 FSH and Testicular Biopsy

Testicular biopsy	*FSH*		
	0-5 u/l (normal range)	*5-15 u/l*	*>15 u/l*
Normal	29	1	
Abnormal biopsy	7	1	2
Maturation arrests			
primary spermatocyte	1	1	
spermatid		1	
Sertoli cells only	1*	3	13

* This man was further investigated with a biopsy of the other testis which confirmed Sertoli cells only on both sides, chromosomes which were normal male and a releasing factor test which showed a normal pituitary response to 100 μg LH/FSHRF.

Testicular Pathology

Thirty of the 60 men had normal testicular histology. The types of pathology encountered in the other 30 men are shown in Table 1.

Chromosomes and Meiotic Analysis

Apart from the chromosomal abnormalities and maturation arrests shown in Table 1, all cases had normal male chromosomes 46XY and normal meiosis.

FSH

Thirty-eight men had a normal serum FSH of less than 5.0 u/l, 7 men had levels between 5.0 and 15 u/l and 15 men had levels greater than 15 u/l. The relationship of the serum FSH levels to testicular biopsy results is shown in Table 2.

Correlation with Physical Examination

The findings on physical examination are shown in relation to the testicular biopsy results in Table 3.

Table 4 shows how the FSH result, when used in conjunction with the findings on physical examination, will predict the biopsy result.

Results of Epididymovasostomy

Seven men with normal testicular histology have had epididymovasostomy. Five men remain azoospermic at 6 months. One had a sperm density of 2 million per ml and 1 a density of 4.4 million per ml. Neither of these men has started a pregnancy.

Discussion

In this series FSH elevation usually indicated severe testicular abnormality, most often Sertoli cells only, or an early maturation arrest. When FSH elevation was associated with small testes severe testicular abnormality was always found and since no treatment is currently available, it would appear reasonable to regard this group as infertile without the need for testicular biopsy. Although complications from a testicular biopsy are few (Ellis, 1968; Meinhard *et al.*, 1973), it is an invasive procedure with potential surgical and anaesthetic complications, and it may cause considerable anxiety.

When the physical examination and FSH assay were normal, 4 of 26 men (15%) had some testicular pathology. The reason the FSH result did not indicate these 4 cases would seem to be that spermatogenesis was proceeding to completion either at a reduced rate or in a patchy fashion, presumably allowing enough feedback to the pituitary to give a normal FSH response. In these

Table 3 Physical Examination and Testicular Biopsy

Findings on physical examination	*Normal biopsy*	*Abnormal biopsy*	*Maturation arrest*	*Sertoli only*
Normal physical examination	23	3	1	
Varicocele	3	1		
Bilateral absence of vas	2	1		
One small testis One normal testis Biopsy from normal side	1	1		
Bilateral small testes	1	4	2	17

Table 4 Physical Examination, FSH Assay and Testicular Biopsy

	Normal biopsy	*Abnormal biopsy*	*Maturation arrest*	*Sertoli only*
Normal examination and FSH <5.0 u/l	22	3	1	
Either abnormality on examination or FSH >5.0 u/l	8	5		1
Small testes FSH >10.0 u/l		2	2	16

cases a testicular biopsy is still necessary to ensure complete accuracy.

There is some doubt as to the exact point in spermatogenesis when feedback to the pituitary occurs. De Kretser *et al.* (1974) found that FSH levels correlated with the number of spermatogonia. In contrast, Johnsen (1970) and Franchimont *et al.* (1972) have suggested that the correlation is between the presence or absence of spermatids. Our own results tend to support de Kretser as there was 1 patient with a meiotic arrest in prophase, *i.e.* primary spermatocyte stage, who had normal FSH levels. There was, however, another patient with Sertoli cells only who also had a normal FSH level and normal pituitary FSH response to releasing factor. These findings suggest that normal feedback may occur despite arrested spermatogenesis before the spermatid stage, but clarification of the mechanism will probably require an Inhibin assay.

It was notable in this study that there was a high incidence of Sertoli cells only (del Castillo syndrome) and of maturation arrest, disorders for which there is no known treatment. Hyperprolactinaemia has been reported to cause some cases of azoospermia (Segal *et al.*, 1976), but in all our cases serum prolactin levels were within normal limits. It will be interesting to examine the findings on testicular histology in a case of azoospermia due to hyperprolactinaemia and in particular to see whether a reversible maturation arrest will be found.

The results of epididymovasostomy in this series using a simple side-to-side anastomosis are disappointing. Bayle (1969) reported a 70% success rate in patency in 650 epididymovasostomy operations and said that 50% of these men started a pregnancy. Many of Bayle's patients had previous venereal disease but none of our patients gave this history. The discrepancy in results is possibly explained by a different aetiology of obstruction. Bayle's figures suggest that in well selected cases epididymovasostomy is a worthwhile procedure.

This work forms part of a thesis to be submitted by T.B.H. to the University of London for the degree of Master of Surgery.

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Immunological Studies of Testicular Tissue in Oligozoospermic and Azoospermic Patients*

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Summary—Testicular biopsies from 6 oligozoospermic and 12 azoospermic patients were examined histologically and immunohistologically. Evidence of maturation arrest and of Type II allergic reactions involving tubular basement membranes was found in all oligozoospermic patients. No evidence of an immune reaction was found in 9 azoospermic patients with maturation arrest. Unilateral or bilateral germ cell aplasia with evidence of mixed Type II and III or Type III and IV reactions was present in 2 oligozoospermic and 2 azoospermic patients.

The findings have been interpreted to indicate that maturation arrest and germ cell aplasia may occasionally be linked in a chain of immunological events, initiated possibly by damage to tubular basement membranes. No correlation was demonstrable between the histological and immunohistological findings and indirect immunofluorescent tests for sperm antibodies. It is suggested that testicular biopsy is a potentially hazardous procedure in the investigation of infertility, and that prepubertal testicular tissues as well as sperm be used as antigens in the immunological investigation of infertility.

The possibility that autoimmunity to spermatozoa may lie behind some cases of male infertility has long been the subject of investigation. Work on immunological barriers to fertility has been extensively reviewed by Schulman (1972) and Hekman and Rümke (1976).

There is no doubt that autoimmunity to spermatozoa is associated with some cases of infertility. Two classes of antibody have been recognised: agglutinating and immobilising on the one hand, and cytotoxic on the other. The former antibodies are responsible for such spermatozoal abnormalities in the ejaculate as agglutination and immobilisation, but they appear not to be responsible for testicular damage. Oligozoospermia and azoospermia can be associated with cytotoxic sperm antibodies while degeneration of germinal epithelium may occur in the absence of such anti-sperm antibodies. This raises the possibility that the putative immune response may be directed against testicular structures other than sperm. The present study was undertaken to explore this possibility.

Testicular biopsies were obtained from oligozoospermic and azoospermic patients attending the Department of Urology for investigation of infertility. Histopathological examination of the biopsies and immunohistological examination for immunoglobulins and complement were carried out by 2 authors working independently. Indirect immunofluorescent tests for sperm antibodies in the serum and routine seminal analyses were performed on specimens of blood and semen obtained prior to biopsy.

Patients and Methods

Eighteen patients were investigated. Following seminal analysis the patients were subjected to testicular biopsy under general anaesthesia. A biopsy from both testes was submitted for histological and immunofluorescent study. The specimens for histology were placed in Bouin's solution while the specimens for immunology were placed in a sterile pot. A sample of 10 ml of blood was taken at the time of the biopsy.

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Tests for sperm antibodies were carried out according to the method of Hjort and Hansen (Rose *et al.*, 1976). The sera were screened at 1:15 dilutions and a polyvalent fluorescein isothiocyanate conjugated antiserum to human immunoglobulins (Burroughs Wellcome) was used at 1:32 dilutions to detect sperm fixing immunoglobulins. The preparations were examined under incident light with a Leitz Orthoplan microscope using filters selective for FITC.

Testicular biopsies were received in the laboratory within 15 min of their removal. Frozen sections prepared from the biopsies were washed, fixed and reacted in direct staining experiments with FITC labelled antisera against human IgG, IgA, IgM, C_3 and $C1_q$. Methods and reagents used to prepare, wash and fix the sections, and to react them with anti-immunoglobulin and anti-complement conjugates have been previously described (Scott *et al.*, 1977).

Results

Of the 18 patients included in this study, 12 were azoospermic and 6 oligozoospermic (Table 1).

The correlation between the seminal analysis, histology and immunofluorescent studies is shown for each patient in Table 2.

Immunofluorescent staining was seen either as a homogeneous linear fluorescence in the basement membrane zone of tubules, or as granular deposits in tubular basement membranes or the walls of blood vessels.

In some instances the testicular interstitium was infiltrated with mononuclear cells. Most of the cells showed no fluorescence, although an occasional cell might show cytoplasmic fluorescence for IgG or IgM.

The changes seen were taken to represent the following 3 types of immune reactions:

Type II (cytotoxic)—homogeneous fluorescence for immunoglobulins and complement.
Type III (immune complex)—granular deposits of immunoglobulins and complement.
Type IV (cell mediated)—infiltration with mononuclear cells, the majority showing no fluorescence.

No immunological significance was placed upon fluorescence for immunoglobulins unaccompanied by fluorescence for complement.

Oligozoospermic Patients

Histological evidence of maturation arrest was found in the testes of all 6 oligozoospermic patients. In 5 patients the basement zone of the tubules showed a Type II (cytotoxic) reaction—homogeneous linear fluorescence for IgG, IgM, C_3 and $C1_q$ with IgG and C_3 predominating. The basement membrane was segmentally involved in 2 patients and uniformly in 3. In the case of the sixth oligozoospermic patient, the basement zone showed homogeneous linear fluorescence for IgG but not for complement.

In 2 oligozoospermic patients immunohistological examination also revealed evidence of a Type III (immune complex) reaction involving the walls of small blood vessels in the testicular interstitium, whilst histopathological features showed maturation arrest in one testis and germ cell aplasia in the other.

Azoospermic Patients

Evidence of maturation arrest was found in 9 cases. Immunofluorescent abnormalities of unknown significance were detected in biopsies from 2 of these 9 patients. In one, a diabetic aged 31 on insulin, the tubular basement membrane zone showed fluorescence for IgG and in the other there was weak IgM fluorescence of testicular epithelium. In neither case was there any fluorescence for C_3 or $C1_q$.

Germ cell aplasia was found in biopsies from 2 azoospermic patients, and the immunohistological findings in both cases pointed to a mixture of allergic reactions. In one, granular deposits of IgG, IgM, C_3 and $C1_q$ were seen in the walls of small blood vessels and a mononuclear infiltrate was present in the interstitium (Type III and Type IV reactions). In the other, there was evidence of a Type II reaction involving tubular basement membranes and of a Type III reaction involving blood vessels.

Normal spermatogenesis was found in association with azoospermia in 1 patient. This patient

Table 1 Clinical Features of Infertile Males

Seminal analysis	*No. of patients*	*Clinical feature*
Azoospermia	2	Unilateral maldescent
	1	Congenital absence of vasa
	2	Prepubertal mumps
	1	Diabetic on insulin
	6	Nil specific
Oligozoospermia	1	Unilateral maldescent
	3	Prepubertal mumps
	2	Nil specific

Table 2 Immunofluorescence, Sperm Antibodies and Spermatogenesis in Azoospermic and Oligozoospermic Patients

Patients	*Immunofluorescence*				*Sperm antibody*	*Spermatogenesis*
	Tubules		*Interstitium*			
	Basement membrane	*Epithelium*	*Blood vessels*	*Mononuclear infiltrate*		
Azoospermic						
1	-	-	-	-	N.D.	M.A.
2	-	-	-	-	-	M.A.
3	-	-	-	-	N.D.	M.A.
4	-	-	-	-	-	M.A.
5	-	-	-	-	+	M.A.
6	-	-	-	-	N.D.	M.A.
7	-	IgM only	-	-	+	M.A.
8	IgG only	-	-	-	-	M.A.
9	-	-	-	-	+	M.A.
10	Type II	-	-	-	-	Normal
11	Type II	-	Type III	-	N.D.	G.C.A.
12	-	-	Type III	Type IV	-	G.C.A.
Oligozoospermic						
13	Type II	-	-	-	N.D.	M.A.
14	Type II	-	-	-	-	M.A.
15	Type II	-	-	-	-	M.A.
16	Type II	-	Type III	-	+	M.A. Unilat-G.C.A.
17	Type II	-	Type III	-	N.D.	M.A. Unilat-G.C.A.
18	IgG only	-	-	-	-	M.A.

M.A. = maturation arrest. G.C.A. = Germ Cell Aplasia.
Type II—homogeneous linear fluorescence } for Ig's *and* complement
Type III—granular fluorescence }
Type IV—infiltration with mononuclear cells showing no fluorescence.

had bilateral absence of the vas deferens. Immunohistologically there was evidence of a weak Type II reaction involving tubular basement membranes.

Anti-sperm Antibodies

Sperm antibody staining was variable and correlated neither with the histological nor with the immunohistological findings in either group of patients (Table 1).

Discussion

This study was undertaken to explore the possibility that testicular constituents other than sperm might be involved in the immunopathogenesis of male infertility.

Evidence of a Type II reaction involving the basement membranes of tubules was found in testicular biopsies from 5 of 6 oligozoospermic patients with maturation arrest. The origin of this reaction is conjectural. Its effects may have been to bring about the maturation arrest by damaging tubular basement membranes and impairing the passage of metabolites and hormones across the membrane.

Evidence of mixed immunological reactions was found in the testes from 2 azoospermic patients with bilateral germ cell aplasia and 2 oligozoospermic patients with unilateral germ cell aplasia. Testes from 1 of the azoospermic patients showed mixed Type III and IV reactions, while testes from the remaining 3 patients showed mixed Type II and III reactions.

Type III reactions, then, were found in association with germ cell aplasia but not in association with maturation arrest. Type II reactions, on the other hand, were found in association with both these conditions. This raises the possibility that maturation arrest and germ cell aplasia may sometimes be linked in a chain of immunological events. It may be that damage to tubular basement membranes allows access of immunocompetent cells to previously sequestered antigens (or vice versa) triggering an autoimmune reaction directed against germ cells.

Twelve azoospermic patients were included in this study and histological evidence of maturation arrest was found in biopsies from 9 of these, but in no case was there any evidence of an immunological reaction in the testes. This observation stands in contrast to the findings in oligozoospermia. It suggests that the cause of maturation arrest in the 2 groups of patients differed, but it does not exclude immune mechanisms in the pathogenesis of maturation arrest in azoospermia. Evidence of immune blockade of androgen receptor sites, for example, would not have been detectable by 2 techniques used here.

Two groups of patients have emerged from this study of oligozoospermia and azoospermia: those in whom testicular biopsies yielded definite evidence of an immune reaction in the testes and those in whom it yielded no such evidence.

The presence or absence of an underlying immune reaction is likely to influence the investigation and treatment of an individual patient. It thus becomes important to be able to detect or exclude immune mechanisms in infertility—preferably by methods not involving biopsy. At least in theory biopsy must carry some risk of initiating or setting the stage for an immune response against sequestered antigens.

In our hands there was no correspondence between the results of indirect immunofluorescent tests for sperm antibodies and the histological and immunohistological findings. We did not look for agglutinating or sperm immobilising antibodies, nor did we use swollen sperm heads in our tests for sperm antibodies. While these tests may have proved more useful than indirect immunofluorescence tests, our findings indicate that testicular tissues other than sperm may be implicated in the immunopathogenesis of infertility. It follows that pre-pubertal testicular tissues might usefully be employed, in addition to sperm, in the immunological investigation of infertility. A complete immunological screen will probably demand tests for antibodies against androgen receptor sites.

Acknowledgements

We thank Mr P. B. Clark and Mr R. E. Williams of the Department of Urology, Leeds General Infirmary, for allowing us to undertake this study on their patients. Our thanks are due also to Mrs P. M. Cave for skilled technical assistance.

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British Journal of Urology (1978), **50**, 423

Case Reports

Renogastric Fistula

Case Report

Mrs M.G., age 51, was admitted with 2 weeks "flu-like" illness associated with colicky lower abdominal pain and occasional vomiting. There was some dysuria but no other urinary symptoms. In 1972 she had reported a similar pain and a normal barium enema examination had been performed. On examination she was clinically pale and unwell and a mass was easily palpable in the left hypochondrium. Investigation revealed a haemoglobin of 11.6 g/dl, white cell count 14.0×10^9/l, E.S.R. 100 mm/h. The urine was infected with bacillus *Proteus* but no tubercle bacilli were seen or cultured. Blood urea and electrolytes were normal. Intravenous urography showed a normal right urinary tract with no function on the left side. Left retrograde pyelography demonstrated an abnormal contracted renal pelvis and the stomach (Fig.). Subsequent barium meal and gastroscopy were both normal.

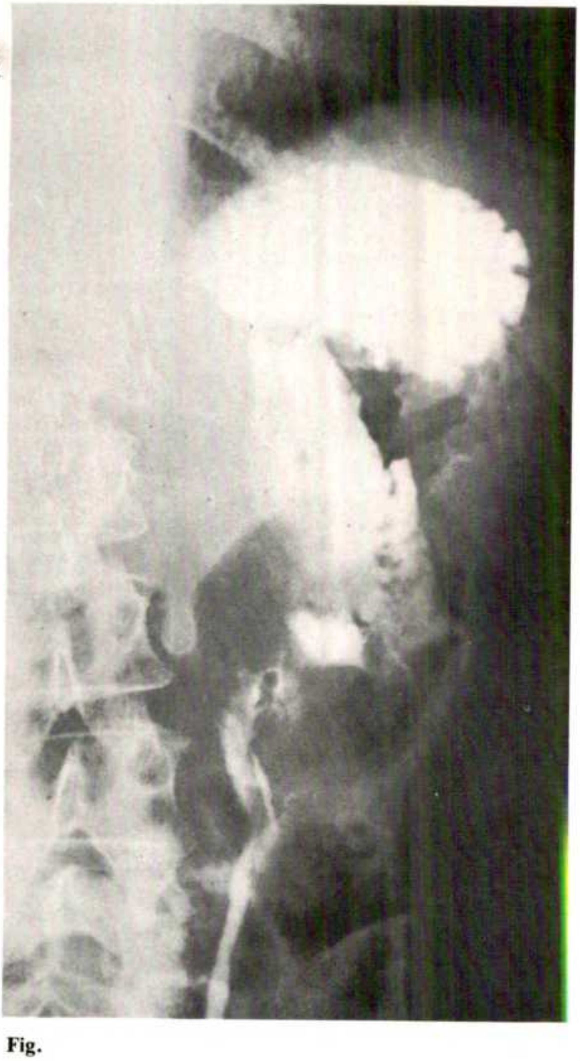

Fig.

The abdominal mass was explored through a left paramedian incision. An abscess cavity was found which was densely adherent to the front of the left kidney, the tail of the pancreas and the posterior wall of the stomach. No fistula could be demonstrated. The abscess was drained and no further procedure undertaken. Culture of pus from the abscess was sterile. Subsequent aortography showed a small atrophic non-functioning left kidney and nephrectomy performed 2 weeks later was uncomplicated. Histology showed non-specific inflammatory changes with no evidence of tuberculosis.

Comment

Reno-gastric fistula is a rarity. Dunn and Kirk (1973) reported a case of their own in association with tuberculosis and reviewed the published cases. Nicholls (1898) described the post-mortem findings in a case of calculous pylonephrosis which had ruptured into the stomach. Collica (1912) reported a further case associated with renal calculi where after nephrectomy a subphrenic abscess ruptured into the stomach.

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G. J. Santer, Walton Hospital, Rice Lane, Liverpool 9.

British Journal of Urology (1978), **50**, 424

Neoplasms of Tunica Vaginalis

Case Report

A 65-year-old patient presented with a right sided fluctuant and transilluminable scrotal swelling that had been present for a year, slowly increasing in size. At operation the hydrocele was opened releasing clear, straw coloured fluid. There were multiple pale pink warty nodules of various sizes from about 2 to 3 mm to 10 mm in diameter distributed over the surface of the testis and the parietal layer of tunica vaginalis.

The nodules had histological features of papilliform epithelial tumours with a fibrous core and few mitotic figures (Fig.). In view of the rarity of this condition opinion was sought from the Testicular Tumour Panel and Registry, who considered that these were papillary mesotheliomata of tunica vaginalis with a fair amount of activity.

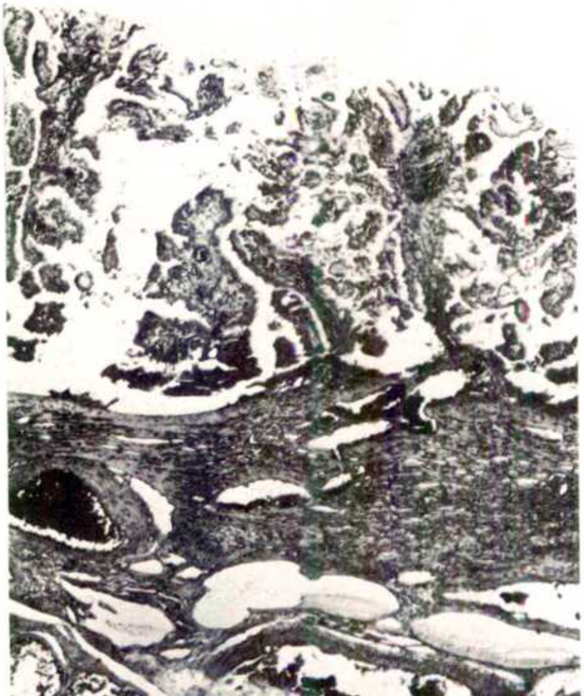

Fig.

The patient remains alive and well 2 years after orchidectomy.

Comment

Neoplasms arising from the tunica vaginalis are very rare. Most present as a simple looking hydrocele making early detection difficult. Even more difficult is the histological diagnosis, perhaps due to their rarity and epithelial-tumour-like appearance. However, since these originate from the mesothelial lining of tunica vaginalis it will be only appropriate to call them mesotheliomata. Similar views have been expressed by Evans (1943), Barbera and Rubino (1957) and Reynolds, Jr. (1958).

Acknowledgements

The author wishes to thank Mr T. G. Gray, Consultant Surgeon, Stonehouse Hospital for his permission to report the case and Dr K. Millar and Dr R. I. Shaw Dunn, Consultant Pathologists for histopathological work. Thanks are also due to Mr A. C. N. Rogers, Consultant Urologist, Falkirk Royal Infirmary for his help in preparing this report and to Mrs E. Gemmell for secretarial assistance.

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British Journal of Urology (1978), **50**, 425

Urethral Syndrome Associated with Chlamydial Infection of the Urethra and Cervix

Case Report

A 21-year-old single girl gave a 3-year history of recurrent increasing frequency and dysuria. She took oral contraceptives and had been treated for gonorrhoea in 1972. There was no significant bacteriuria or pyuria. All other investigations were normal. Cystoscopy revealed only intense urethritis with some basal cystitis.

At the Department of Sexually Transmitted Diseases, oedema of the length of the urethra was palpated through the anterior vaginal wall and discharge was expressed on massage (Fig.). A large hypertrophic erosion and endo-cervical mucopus were found. *Chlamydia trachomatis* was isolated from the urethra and cervix and all other microbiological investigations were negative.

After 21 days oxytetracycline (250 mg 6-hourly) she became symptom-free. The urethral oedema and discharge were minimal, clear mucus was present in the endocervix and the oedema and congestion of the cervical erosion had disappeared, *i.e.*, the hypertrophic erosion had become simple. Follow-up cultures for chlamydia remained negative for a year. Urethral *Chlamydia trachomatis* culture from her consort was negative due, possibly, to recent antibiotic therapy.

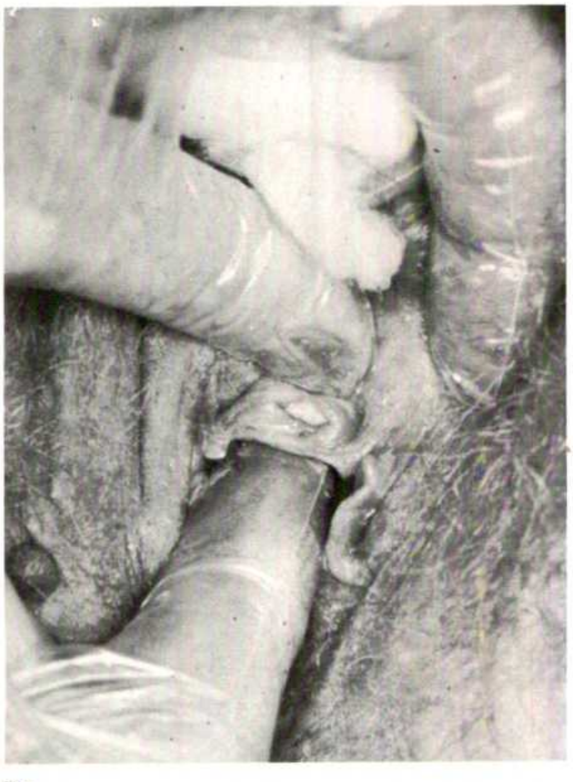

Fig.

Comment

Chlamydia trachomatis has been isolated from 50% of men with non-gonococcal urethritis and in one-third of their female partners (Hilton *et al.*, 1974). Its possible role in prostatitis, epididymitis and salpingitis has not yet been evaluated. Dunlop *et al.* (1972) reported the first isolation of chlamydia from the female urethra in a patient who was examined because her husband had a 6-month history of chlamydial kerato-conjunctivitis. She had recurrent dysuria and frequency. The association of chlamydial infection of the cervix with hypertrophic (oedematous and congested) erosion and endocervical mucopus has been reported (Rees *et al.*, 1977).

This case is of interest in that co-existing urethritis and cervicitis was observed by the urologist and that chlamydia was isolated from both sites. It is suggested that the possible association of chlamydial infection with the urethral syndrome requires further investigation.

Acknowledgements

We are indebted to Dr D. Hobson for the culture of *Chlamydia trachomatis* and to Dr Alan Percival for microbiological investigations.

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British Journal of Urology (1978), **50**, 426

Fracture of the Penis

Seventy-eight cases of this injury have been previously reported in the Western literature.

Case Report

A 49-year-old man presented with severe pain in a grossly swollen and deformed penis (Fig.). The patient was unable to micturate spontaneously and there was no urethral bleeding. During intercourse, the patient standing and his wife lying on the bed, the carpet had slipped causing the patient to fall and strike his erect organ against the bed frame.

The condition was managed conservatively, except for a suprapubic cystotomy being performed under general anaesthetic to relieve the acute retention. On the second day he micturated spontaneously, and at 2 weeks the catheter was removed and the patient discharged.

Five weeks after the accident, his erection was straight and the penis appeared normal except for a "dewlap" on the phrenum caused by oedematous skin. At 6 months, intercourse was normal if less ambitious and the patient was discharged.

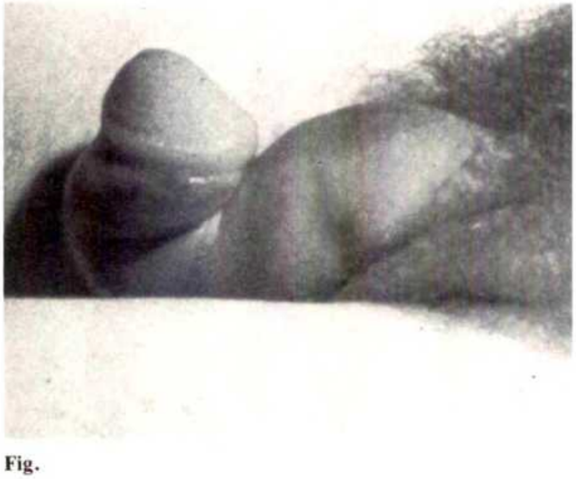

Fig.

Comment

Fracture of the penis only occurs if the organ is erect and modes of injury include: blunt trauma, spontaneous occurrence during sexual intercourse, forcibly bending the erection, for example in fending off would be rapists.

Treatment can be either conservative or surgical. Thompson (1954) advocated conservative treatment, operative intervention being required only for drainage of the haematoma if gangrene of the penis threatens. More recently surgical exploration has been encouraged as it allows drainage of the haematoma and repair of the urethra and Tunica Albuginea (Anderson and Pless, 1976).

Acknowledgements

We would like to thank Mr R. S. Murley for his wise guidance in managing this case and permission to publish it (also to Dr L. McElwain for his photography, the Department of Medical Illustration, Queen Victoria Hospital, East Grinstead and Mrs J. Weeks for her secretarial assistance).

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British Journal of Urology (1978), **50**, 427

A Case of Ureteral Diverticula

Case Report

A 37-year-old male patient presented with right lumbar pain not accompanied by fever or urinary symptoms. Physical examination was normal, the lumbar pain being aggravated by movement of the trunk. Routine blood and urine tests were normal, no urinary infection being detected. IVP showed that the right pelvis and ureter were normal, but on the left side a diverticular image was seen in the pelvic ureter; on oblique films it was clear that there were 2 diverticula. The lumbar pain ceased rapidly with symptomatic medication. No therapy was instituted for the diverticula, nor any further examination was attempted; we only advised a periodic surveillance.

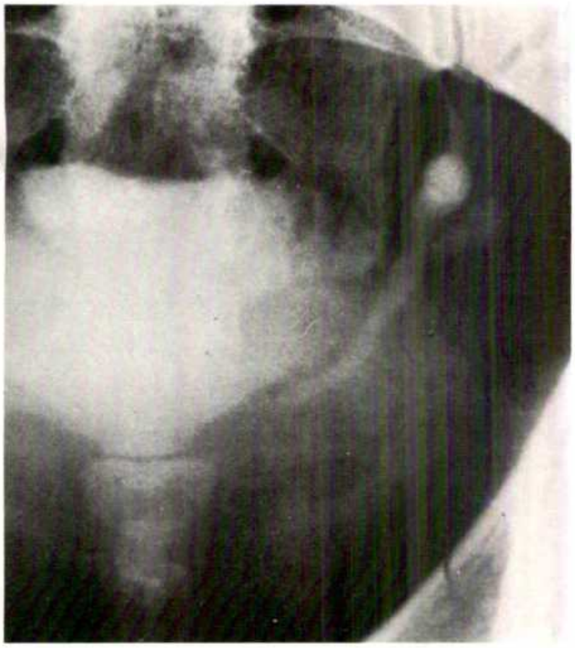

Fig.

Comment

Despite lack of awareness of their existence, ureteral diverticula are a very infrequent situation, and no one has a sufficient number of well documented cases to permit a definitive answer concerning the criteria of classification and etiologic nature (Rank *et al.*, 1960; Crumplin and Jones, 1972). Nevertheless the present case is, with great probability a congenital developmental anomaly, and may well be considered as the blind endings of an incompletely formed double or triple ureter.

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British Journal of Urology (1978), **50**, 428

Torsion of the Mesorchium—The Testis Twisted upon the Epididymis

Case Report

A 12-year-old Japanese boy was admitted with a tender swelling of 2 weeks' duration in the left scrotal region. Antibiotics had been given without effect at another hospital with a diagnosis of epididymitis. On palpation, there was a mass in the left scrotum, the size of a hen's egg, retracted to its upper region as compared with that of the opposite side. The testis and the epididymis could not be separated. The white blood cell count was not elevated and the remainder of the physical examination was normal.

By opening the tunica vaginalis, the testis twisted upon the epididymis which had relatively strong adhesion to its neighbouring tissue. The testis was dark red and swollen, in attachment to the epididymis only at the globus mayor.

Incision of the testis showed haemorrhagic infarction. Left orchidectomy was carried out.

Histological examination showed gangrene of the testis, whereas the epididymis appeared almost normal (Figs. 1 and 2).

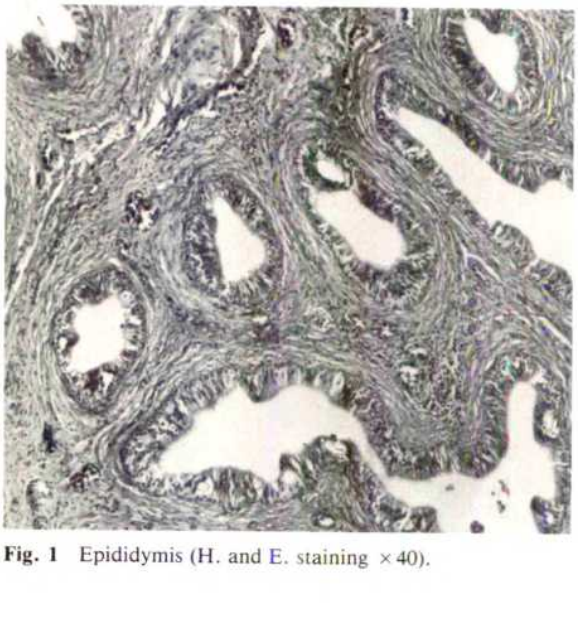

Fig. 1 Epididymis (H. and E. staining ×40).

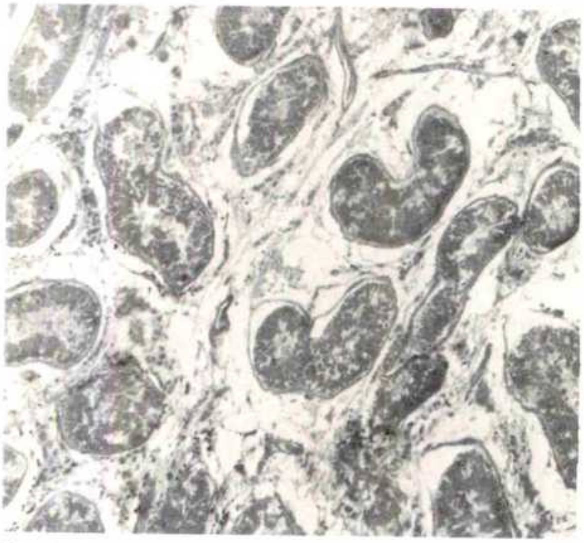

Fig. 2 Testis (H. and E. staining ×40).

Comment

Torsion of the spermatic cord has a relatively high incidence among prepubertal children (Williamson, 1976), whereas torsion of the mesorchium—the testis twisted upon the epididymis—is very rare.

In our case, a fundamental anatomical abnormality, namely the testis detached from the epididymis except at the globus major, was thought to be an aetiological factor.

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British Journal of Urology (1978), **50**, 429

Spermatic Cord Liposarcoma

Case Report

A 77-year-old man was referred to the hospital with a month's history of a painless swelling in the left side of the scrotum. On examination there was a goose-egg-sized, firm with rubbery consistency, smooth but slightly lobulated mass in the scrotum which did not transilluminate. Left orchidectomy with high ligation of the spermatic cord was performed. Exploration showed 2 tumour masses, separated from each other, which appeared to be arising from the spermatic cord (Fig. 1). The testis was normal. Microscopically 2 masses presented essentially the same features. They were composed of adult fat admixed with collagenous connective tissue. Intermingled among them were large lipoblasts with foamy cytoplasm and bizarre giant cells with deep-staining nuclei. Diagnosis: well differentiated liposarcoma (Fig. 2). Convalescence was uneventful but he died elsewhere 1 month later due to heart failure.

Comment

Among the soft tissue sarcomas, liposarcoma is one of the more common malignant tumours (Stout and Lattes, 1967). But liposarcoma of the spermatic cord is extremely rare (Datta *et al.*, 1971; Mackenzie and Roberts, 1974).

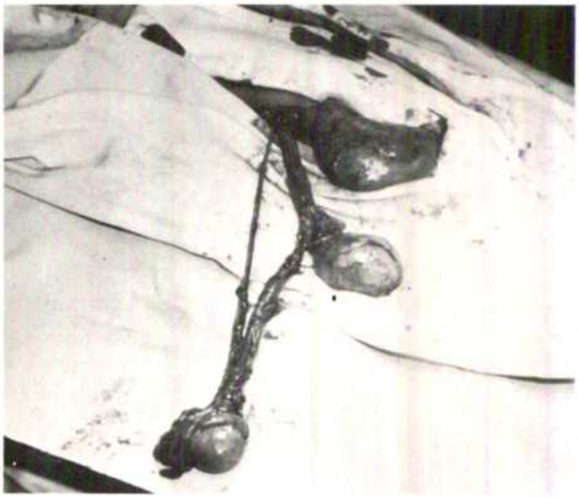

Fig. 1 Photograph showing a large tumour mass arising from the region of the external inguinal ring and smaller one from the middle portion of the spermatic cord.

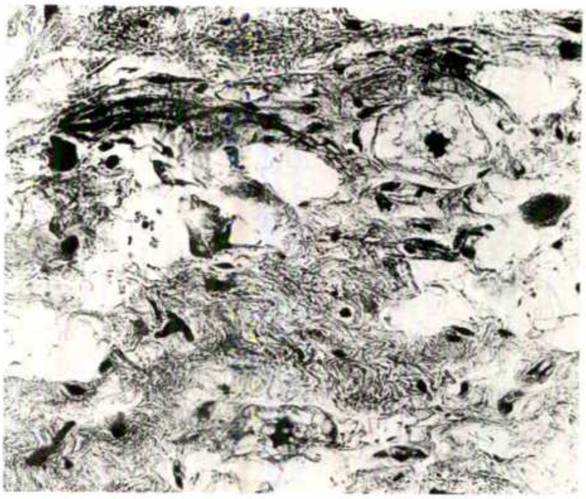

Fig. 2 Photomicrograph showing large lipoblasts with foamy cytoplasm and bizarre giant cells with deep-staining nuclei (H. and E. ×200).

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British Journal of Urology (1978), **50**, 430

An Isolated Injury of Right Renal Artery Due to Blunt Trauma

Introduction

Renal trauma is usually mild, with transient haematuria and no active surgical treatment is required. But occasionally, severe haemorrhage and shock demands active surgical management. Renal pedicle injuries due to closed trauma are fortunately rare, the majority being due to penetrating trauma. Guerreiro *et al.* (1971) analysed 33 patients with renal pedicle injuries, of whom only 6 were due to blunt trauma, involving the artery or vein in isolation or together. But they remarked that the right renal artery was never injured alone.

Case Report

A 17-year-old male, was admitted after a motorcycle accident with multiple lacerations and a fractured mandible and skull. He was conscious, with BP 110/60 mmHg. He was tender in both flanks guarded and slightly distended. He was catheterised but without haematuria. Abdominal X-ray showed absence of the right psoas shadow. About 15 min later, he became clinically shocked BP 80/60 mmHg. He was resuscitated and at laparotomy, it was found that the right renal artery had avulsed at its radicles, the kidney hanging loose in a huge haematoma by its vein and ureter. A nephrectomy was performed and he subsequently recovered.

Comment

This case was interesting not only because it is the first reported one but also because kidney injury was not suspected pre-operatively because of absence of haematuria. The mechanism for such an injury must be sudden deceleration, the artery being more rigid and fixed than the vein and ureter, probably avulsing from the mobile kidney on impact to the anterior abdominal wall. Cases of traumatic severance of renal pedicle without death have been reported by Knappenberger *et al.* (1963), and Watkins *et al.* (1967), among others.

Acknowledgements

My thanks go to Mr A. D. Messent, Consultant Surgeon at Haroldwood Hospital, who performed the operation, for allowing me to publish this paper, also Mrs C. A. Paul for her assistance.

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British Journal of Urology (1978), **50**, 431

Book Reviews

Progress in Lymphology. Edited by R. C. Mayall and Marlys H. Witte. Pp. xiv + 389. New York: Plenum Press, 1977. $47.40.

This book comprises 51 selected papers from the Fourth (1973) and Fifth (1975) International Congresses of Lymphology. The text is therefore a varied and highly selected summary of current work on the lymphatic system. Several papers concern urological topics. Many others are of general interest but this book is too expensive and too limited for individuals to purchase. Not one of the papers is from the United Kingdom—was this lack of interest, quality or air fare?—the interested reader will make his own judgement.

Colloquium on Renal Lithiasis. Edited by B. Finlayson and W. C. Thomas. Pp. xiv + 370. Florida: University Presses of Florida, 1977. $25.00.

This is a most useful book for those engaged in stone research. There are 37 papers from a wide range of experts in many disciplines. These papers show that stone formation is not simply a result of excessive saturation of the urine with one solute and that low calcium diet is no longer the logical treatment for all cases!

The answer to stone disease is not to be found here but these contributions from epidemiologists, gastroenterologists, chemists, crystallographers, urine inhibition and urine saturation experts, as well as clinicians involved in the care of stone patients, may be a glimmer of light at the end of the tunnel. There is a strong clinical orientation and most papers will be comprehensible to the clinician.

It is a pity that the Proceedings of this Colloquium held in 1975 at Gainesville, Florida have taken so long to be published.

Transactions of the American Association of Genito-Urinary Surgeons. Volume 68. Pp. 137. Baltimore: Williams & Wilkins Co., 1976. $15.00 (£10.50 approx.)

The Active Members of the American Association of Genito-Urinary Surgeons consist of most heads of departments and senior urologists in North America; the Corresponding Members are leading urologists in most western countries. This formidable group meet annually and the Transactions of the meeting are reported in a format similar to that of the *Journal of Urology*. However, an important difference lies in the Discussion sections: most of these are well worth reading, some are illuminating and often contain some very sharp but fair comment. The range of presentations is wide, so that here is an up-to-date slice of urology which would be a very useful volume for a departmental library.

British Journal of Urology (1978), **50**, 432

Conferences and Courses

Institute of Urology (The University of London)

Programme of Seminars for 1978/79

1978
8 November: Vasectomy
9-11 November: Paediatric Urology
8-9 December: Uro-radiology weekend

1979
26-27 January: Urodynamics
12-23 February: British Council Course—Urological Malignancies
16-17 March: Urology for FRCS
March (date to be arranged): Genito-urinary infections
April (date to be arranged): Renal diseases in pregnancy
May (date to be arranged): 1-week course in Operative Surgery
June (date to be arranged): Urological Malignancies
March-May (date to be arranged): 3-month course covering the whole range of Urological Practice

Further details from: The Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2. Telephone: 01-836 5361.

International Conference on Urinary Calculi

Perth, Western Australia. 4-8 August 1979.

The Conference will include sessions on: Theories of Stone Formation, The Epidemiology of Stone Diseases, Metabolic Inter-relationships, Medical and Surgical Treatment, Prevention of Stone Formation.

Further information from: Assoc. Professor J. G. Brockis, International Conference on Urinary Calculi, University Department of Surgery, Royal Perth Hospital, Box X2213, G.P.O., Perth, Western Australia 6001.

British Association of Urological Surgeons: Annual Meeting

Bristol. 4-7 July 1979.

Those wishing to present a paper or a film should submit an abstract on A4 paper, 25 copies, to the Honorary Secretary, The British Association of Urological Surgeons, at the Royal College of Surgeons, 35-43 Lincoln's Inn Fields, London WC2A 3PN, not later than 5 January 1979.

One-day Provincial Meeting: BAUS

Nottingham. 7 October 1978.

Further particulars from: Honorary Secretary, BAUS, Royal College of Surgeons, Lincoln's Inn Fields, London WC2.

Request for Informal Proposals on Contraceptive Research and Development

The Program for Applied Research on Fertility Regulation (PARFR) at Northwestern University, Chicago, Illinois, is soliciting informal proposals from foreign and United States institutions for *Applied Research* projects in the field of fertility control. Proposals incorporating new ideas, techniques, and procedures, with the objective of developing new or improved methods of fertility control appropriate for use in developing countries will receive priority consideration. PARFR's interest in contraception includes the full range of fertility control methods—hormonal and other pharmacologic agents, mechanical and surgical. Contraceptive methods proposed for research support should be close to the stage of clinical applicability, although projects could include laboratory, animal and/or human investigation.

Further information can be obtained by writing or calling: Director of Administration, Program for Applied Research on Fertility Regulation, 1040 Passavant Pavilion, 303 East Superior Street, Chicago, Illinois 60611, USA. Telephone: (312) 649-2990.

Organisers wishing to have details of their courses and conferences published in the Journal should send details to J. E. Newsam, Western General Hospital, Edinburgh EH4 2XU.

CURRENT UROLOGICAL LITERATURE: SELECT BIBLIOGRAPHY[1]

The List of Current Urological Literature is now arranged to correspond to the order in which papers are published in the *Journal*, i.e. in anatomical order beginning with papers on the kidney.

A general section is included at the end.

KIDNEY

Congenital Anomalies. Electron microscopic findings of familial hereditary nephropathy. Cases differing from Alport's syndrome. (Y. Fukunishi *et al.*) *Ann. Paediatr. Jpn.* 1977, **22**, 55.

Duplication of the renal collecting system with hypoplasia of the upper pole of the kidney. (G. Cappellini *et al.*) *Acta Radiol.* 1977, **18**, 663.

Bilateral pelvic ectopic kidneys. (J. Fischelovitch and J. Jancu.) *Br. J. Urol.* 1978, **50**, 51.

Diagnostics of malformations of the kidneys and the upper urinary tract. (R. A. Parsi *et al.*) *Dtsch. Gesundh.* 1978, **33**, 206.

Renal anomalies on the "XY female". (J. A. Swanson and F. K. Chapler.) *Obstet. Gynecol.* 1978, **51**, 237.

Unilateral horseshoe kidney with contralaterally dead-end ureter. (I. Fraser and D. Thomas.) *Aktuel. Urol.* 1978, 9, 11.

Abdominal aortic aneurysm with rupture into inferior cava associated with horseshoe kidney. (R. G. Landes *et al.*) *Ann. Surg.* 1978, **187**, 329.

Congenital renal abnormalities in the Laurence-Moon-Biedl syndrome. (N. H. Bluett *et al.*) *Arch. Dis. Child.* 1977, **52**, 968.

Crossed renal ectopia with a single kidney: angiographic findings in 2 cases. (I. P. Landa *et al.*) *Radiologia,* 1977, **19**, 435.

The report of 23 cases of complete duplex system of the urinary tract: retrospective analyses of their clinical features, pathologic physiology, surgical management and embryology. (T. Koyanagi and I. Tsuji.) *Jpn. J. Urol.* 1977, **68**, 1218.

Sigmoid kidney accompanied by the absence of uterine tubes, uterus and vagina. (L. Kontogeorgos.) *J. Urol. Néphrol.* 1977, **83**, 813.

Renal dysplasia in children. (L. Boccon-Gibod and J. Petit.) *Ann. Urol.* 1977, **11**, 171.

Antenatal diagnosis of congenital nephrosis of the Finnish type. (B. Kjessler *et al.*) *Acta Obstet. Gynecol. Scand.* Suppl. 69, 1977, 59.

Study of a family with hereditary nephritis (Alport's syndrome). (R. Marcenletosa *et al.*) *Rev. Clin. Esp.* 1977, **147**, 291.

Hereditary nephritis: a re-examination of its clinical and genetic features. (W. M. O'Neill *et al.*) *Ann. Intern. Med.* 1978, **88**, 176.

Congenital arteriovenous fistula of the kidney. (T. C. Sharma.) *Int. Surg.* 1977, **62**, 543.

Medullary hypertrophy of the kidney. (A. Puigvert.) *J. Urol. Néphrol.* 1978, **84**, 41.

Bilateral renal aplasia without Potter's syndrome. (O. Hjalmarson and K. G. Sabel.) *Acta Paediatr. Scand.* 1978, **67**, 113.

A case of thoracic kidney in a child. (P. Georgacopulo *et al.*) *Minerva Chir.* 1977, **32**, 1349.

Surgery of congenital urinary tract disease. (D. I. Williams.) *Proc. R. Soc. Med.* 1977, **70**, 832.

Trauma. Renal trauma. (R. Mendez.) *J. Urol.* 1977, **118**, 698.

Importance of scanning in the diagnosis of renal traumas in infancy. (G. C. Mussa *et al.*) *Minerva Pediatr.* 1978, **30**, 199.

Organ preservation in contusion of kidneys. (W. Leisering.) *Zentralbl. Chir.* 1977, **102**, 1307.

Spontaneous rupture of the renal pelvis. A non-surgical acute abdomen. (M. Prémont *et al.*) *Nouv. Presse Méd.* 1978, **7**, 643.

Renal injury by companion kidney during hypothermic pulsatile perfusion. (C. B. Anderson *et al.*) *Surgery,* 1978, **83**, 72.

Kidney trauma in a 13 years old child with voluminous bilateral hydronephrosis. (J. Leemans and A. Kotowicz.) *J. Urol. Néphrol.* 1977, **83**, 817.

Traumatic rupture of the isthmus of a horseshoe kidney. (C. Kontogeorgos.) *J. Urol. Néphrol.* 1977, **83**, 821.

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Results of non-operative management of blunt renal trauma. (I. M. Thompson *et al.*) *J. Urol.* 1977, **118**, 522.

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Infections. Pediatric hypertension as delayed sequela of reflux-induced chronic pyelonephritis. (J. F. Stecker *et al.*) *J. Urol.* 1977, **118**, 644.

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[1] Titles in this list have been taken from those listed in *Current Contents: Clinical Practice* published by Institute for Scientific Information, Philadelphia.

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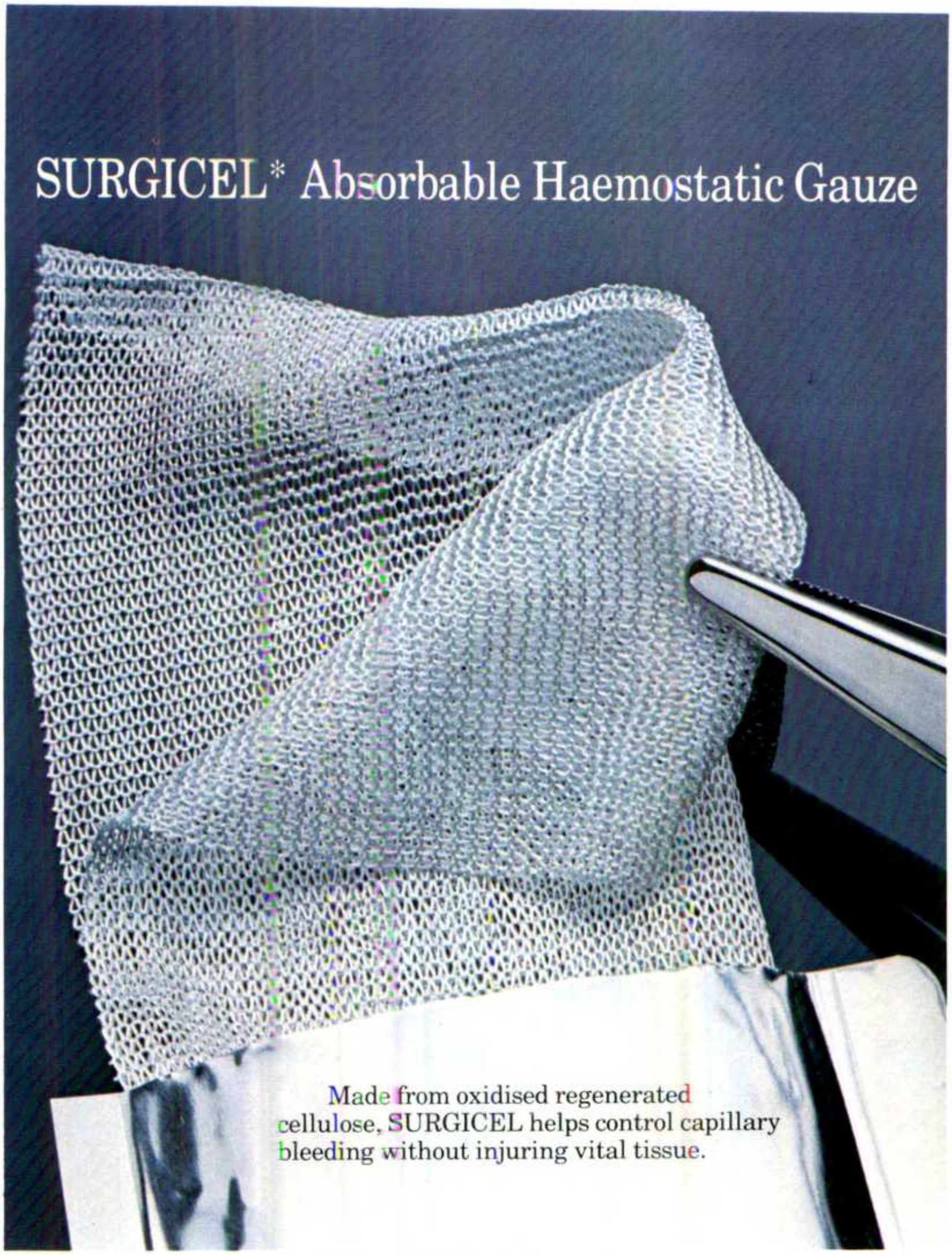

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Case Reports

423 Renogastric Fistula
M. A. P. Milling and G. J. Santer

424 Neoplasms of Tunica Vaginalis
A. P. Sinha

425 Urethral Syndrome Associated with Chlamydial Infection of the Urethra and Cervix
I. Anne Tait, Elisabeth Rees and R. M. Jameson

426 Fracture of the Penis
D. M. Davies and I. Mitchell

427 A Case of Ureteral Diverticula
H. A. De Carvalho

428 Torsion of the Mesorchium—the Testis Twisted upon the Epididymis
M. Oka, K. Nakashima and R. Sakoda

429 Spermatic Cord Liposarcoma
K. Senoh, Y. Osada and J. Kawachi

430 An Isolated Injury of Right Renal Artery Due to Blunt Trauma
Charles Atimomo

431 Book Reviews

432 Conferences and Courses

xxxiii Current Urological Literature: Select Bibliography

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British Journal of Urology

October 1978 Volume 50 Number 6

Original Articles

361 Report of the Standing Committee on Urological Instruments: Endoscopes
J. P. Mitchell, J. Blandy, J. G. Gow, C. H. Kinder, R. T. Turner-Warwick and J. F. R. Withycombe

367 Renal Growth Following Reimplantation of the Ureters for Reflux
J. D. Atwell and M. R. Vijay

371 An Evaluation of Techniques Used for the Production of Temporary Renal Ischaemia
G. A. McLoughlin, M. R. Heal and I. M. Tyrell

376 The Pattern of Urolithiasis in the Sudan
A. Kambal, S. M. A. Wahab and A. H. Khattas

378 Uretero-Neo-Cystostomy in Renal Transplantation. Is an Antireflux Mechanism Mandatory?
F. M. J. Debruyne, P. G. A. B. Wijdeveld, R. A. P. Koene, M. L. Chafik, W. A. Moonen and G. A. M. Renders

383 Reimplantation of the Wide Ureter
M. C. Bishop, A. R. Askew and J. C. Smith

387 The Behaviour of the Bladder During Physical Activity
E. D. James

395 Bladder Neck Incision—a Treatment for Retention with Overflow in the Absence of Adenoma
J. D. Jenkins and N. H. Allen

398 The Effect of Pelvic Nerve Stimulation and Some Drugs on the Urethra and Bladder of the Dog
K. E. Creed and A. G. S. Tulloch

406 The Effect on the Bladder Pressure of Sudden Entry of Fluid into the Posterior Urethra
J. R. Sutherst and M. Brown

410 One-stage Excision Urethroplasty for Stricture
A. Panagakis, J. C. Smith and J. L. Williams

415 Can Follicle Stimulating Hormone Estimation Replace Testicular Biopsy in the Diagnosis of Obstructive Azoospermia?
T. B. Hargreave and A. M. Jequier

419 Immunological Studies of Testicular Tissue in Oligozoospermic and Azoospermic Patients
T. A. Taylor, D. G. Scott, C. K. Anderson, N. Jones and P. A. H. Stewart

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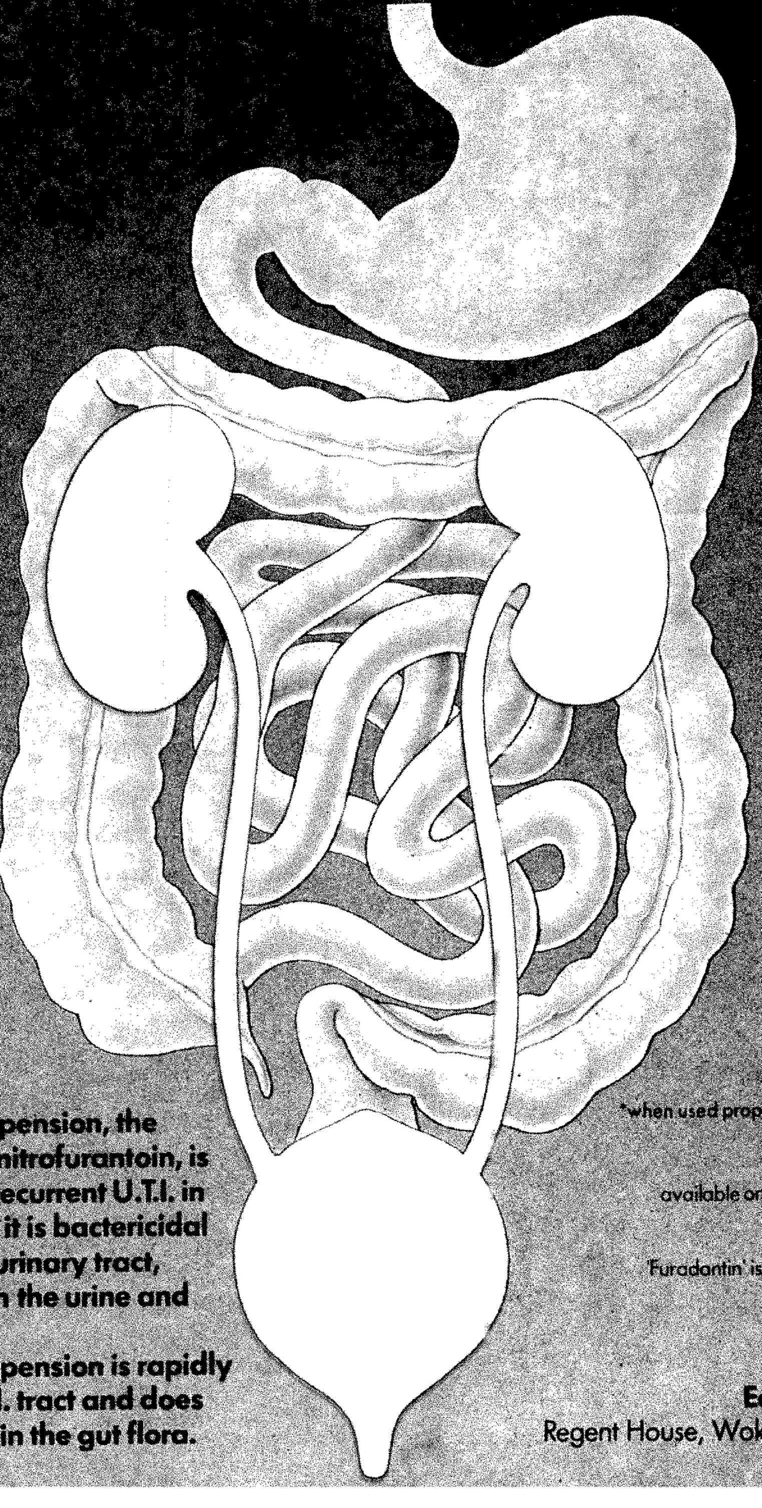

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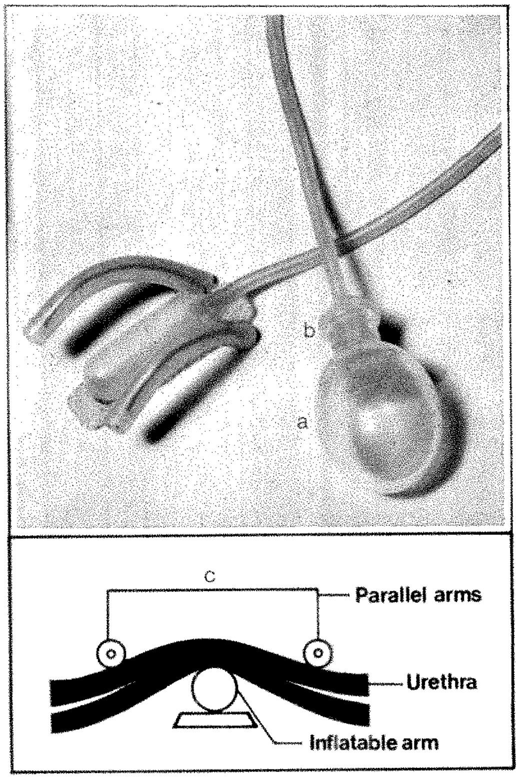

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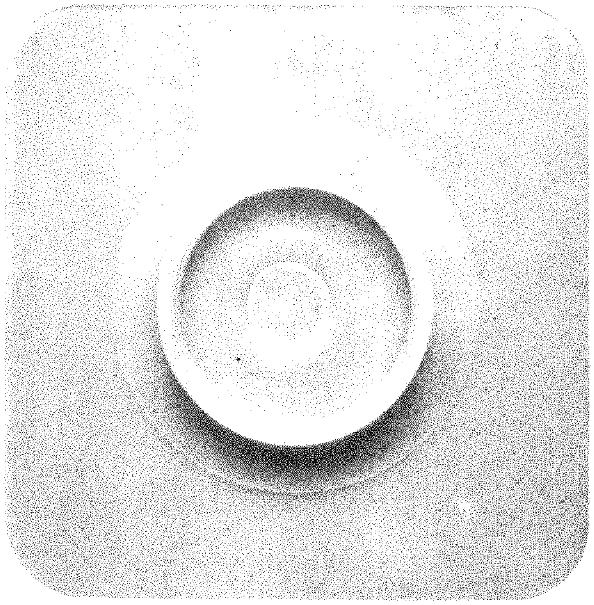

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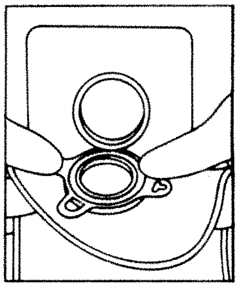

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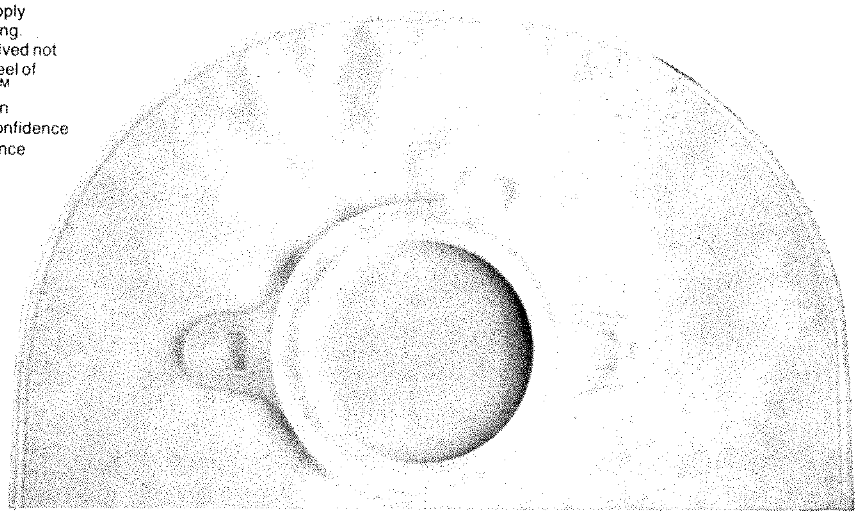

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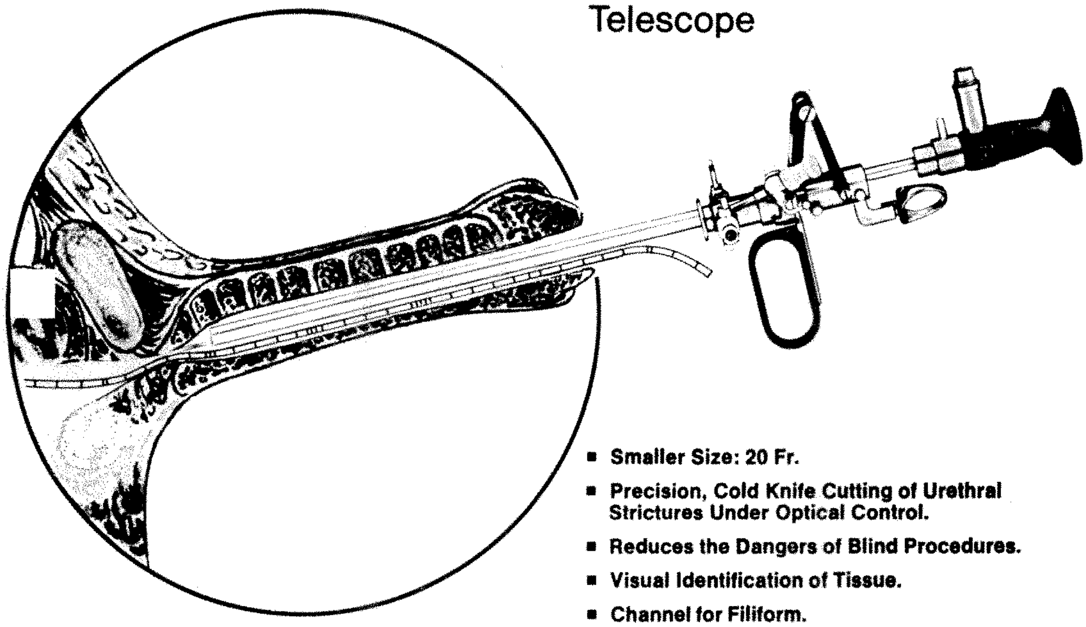

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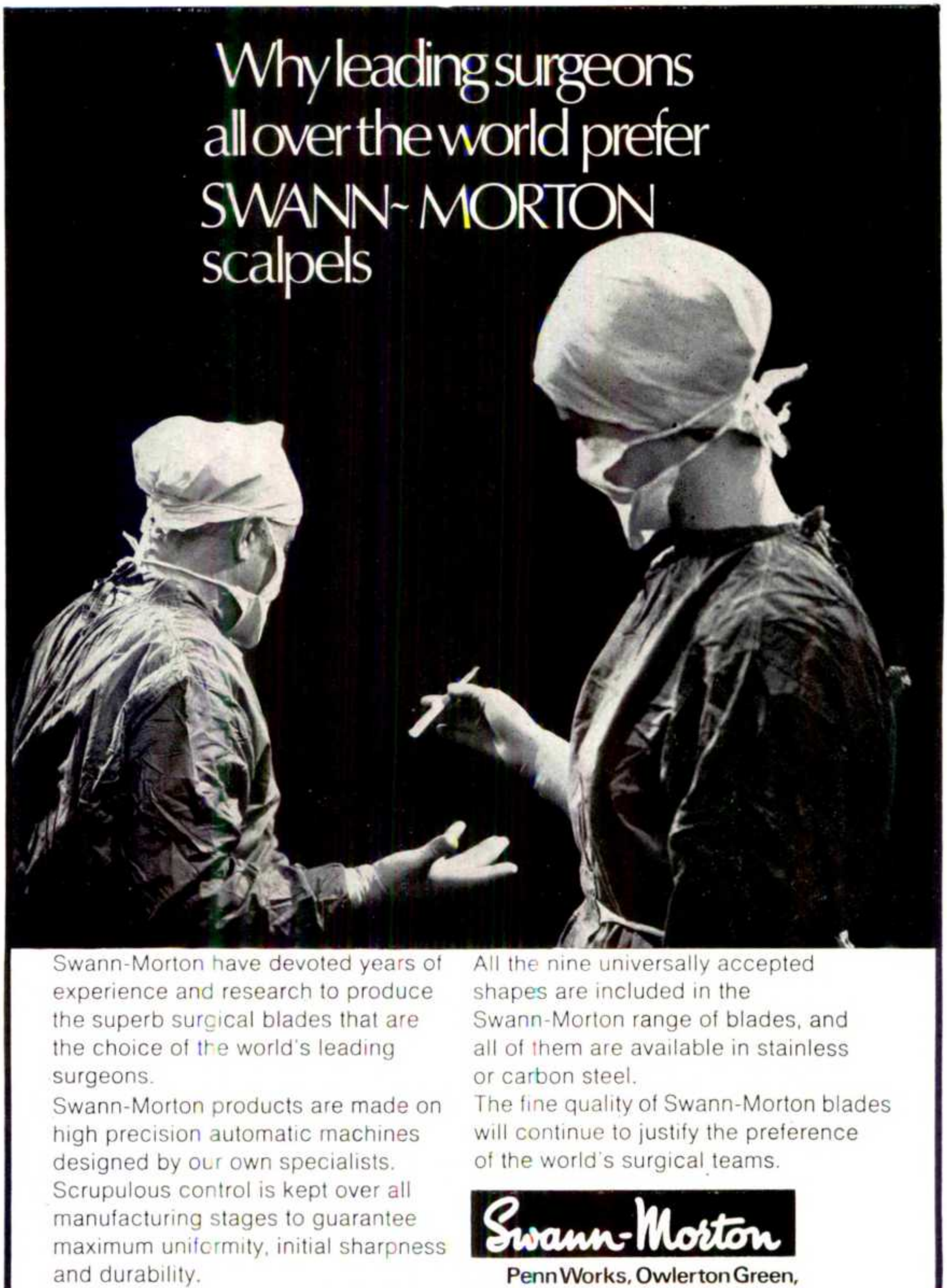

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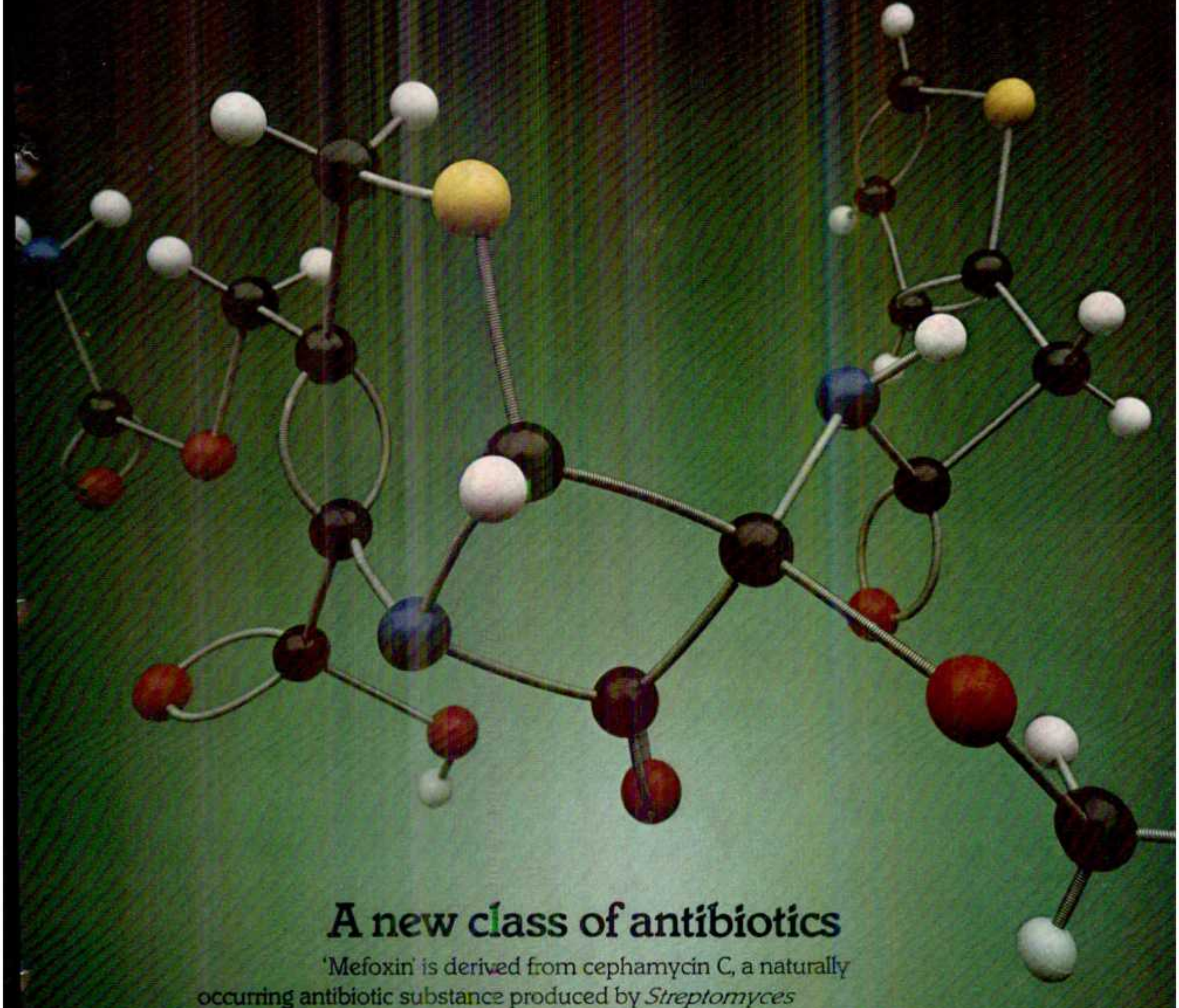
Cefoxitin sodium, MSD

INJECTION

First of the cephamycins

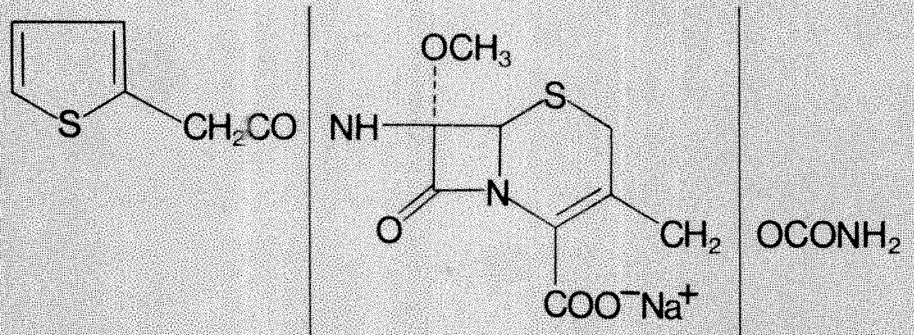


A new class of antibiotics

'Mefoxin' is derived from cephamycin C, a naturally occurring antibiotic substance produced by *Streptomyces lactamdurans*. This naturally occurring antibiotic has been modified in the MSD Research Laboratories to enhance its therapeutic usefulness.

Prescribing information overleaf

'Mefoxin' has a unique molecular structure offering outstanding clinical benefits and a specific clinical profile.



Thienylacetyl side-chain:
enhances activity against Gram-positive pathogens

Cephamycin nucleus:
provides bactericidal activity against a wide range of pathogens, Gram-negative in particular. 7α-methoxy group protects against β-lactamase degradation

Carbamoyloxy side-chain:
protects antibiotic from being metabolised

▼Prescribing information

Indications

'Mefoxin' is a broad-spectrum bactericidal antibiotic indicated for the treatment of infections caused by susceptible strains of Gram-positive and Gram-negative pathogens both aerobic and anaerobic.

'Mefoxin' has been clinically effective not only in infections due to antibiotic-sensitive organisms, but also in infections due to organisms resistant to one or more of the following antibacterial agents: penicillin, ampicillin, carbenicillin, tetracyclines, erythromycin, chloramphenicol, cephalosporins, kanamycin, gentamicin, tobramycin and sulphamethoxazole-trimethoprim.

Many Gram-negative pathogens are resistant to penicillins and cephalosporins through the action of the β-lactamases which are produced by these pathogens. 'Mefoxin' is remarkably stable in the presence of these bacterial β-lactamases, both penicillinases and cephalosporinases. Hence, the clinical efficacy of 'Mefoxin' extends to many infections caused by such pathogens.

'Mefoxin' is indicated for the treatment of the following infections caused by sensitive bacteria:
Peritonitis and other intra-abdominal and intrapelvic infections; female genital tract infections; septicaemia; urinary tract infections; respiratory tract infections; bone and joint infections; and skin and soft tissue infections.

'Mefoxin' is indicated for adjunctive therapy in the surgical treatment of infections, including abscesses, infection complicating hollow visceral perforations, cutaneous infections, and infections of serous surfaces, whether caused by aerobes, mixed aerobes and anaerobes, or anaerobes.

Microbiology

'Mefoxin' is active *in vitro* against:

Aerobic bacteria

Gram-positive cocci including: Staphylococci (including coagulase-positive, coagulase-negative and penicillinase-producing strains), Group A beta-haemolytic streptococci (*Streptococcus pyogenes*), Group B beta-haemolytic streptococci (*Streptococcus agalactiae*), *Streptococcus pneumoniae* (*Diplococcus pneumoniae*), other streptococci (except group D streptococci including enterococci, most strains of which are resistant, e.g. *Streptococcus faecalis*). *Gram-negative cocci including: Neisseria gonorrhoeae* (including penicillinase-producing strains), *Neisseria meningitidis*; *Gram-negative rods, facultative anaerobes including: Escherichia coli, Klebsiella pneumoniae, Klebsiella* spp., *Proteus mirabilis, Proteus* (indole-positive): *Proteus vulgaris, Proteus rettgeri, Proteus morganii, Haemophilus influenzae, Serratia marcescens, Providencia* spp., *Salmonella* and *Shigella* spp.

Anaerobic bacteria

Gram-positive cocci including: Peptococcus spp., *Peptostreptococcus* spp., Micro-aerophilic streptococcus; *Gram-positive rods including: Clostridium perfringens, Clostridium* spp., *Eubacterium* spp., *Propionibacterium acnes*; *Gram-negative cocci including: Veillonella* spp.; *Gram-negative rods including: Bacteroides fragilis, Bacteroides melaninogenicus, Bacteroides* spp. including both penicillin-sensitive and penicillin-resistant strains, *Fusobacterium* spp.

'Mefoxin' is active against some strains of the following bacteria: *Acinetobacter calcoaceticus var. anitratum* (*Herellea vaginicola*), *Acinetobacter calcoaceticus var. lwoffii* (*Mima polymorpha*), *Alcaligenes faecalis, Citrobacter* spp. and *Flavobacterium* spp., *Enterobacter* spp.

'Mefoxin' is not active against *Pseudomonas*, most strains of enterococci and many strains of *Enterobacter cloacae*.

Dosage and administration

'Mefoxin' may be administered intravenously or intramuscularly (see reconstitution directions for each route below). Dosage and route of administration should be determined by severity of infection, susceptibility of the causative organism, and condition of the patient.

Therapy may be started while awaiting the results of susceptibility testing.

Dosage: The usual adult dosage is 1 g to 2 g of 'Mefoxin' every eight hours. (See chart.)

In adults with renal insufficiency, an initial loading dose of 1 g to 2 g may be given. After a loading dose, the following recommendations for maintenance dosage may be used as a guide.

Usual adult dosage

Type of infection	Dose	Frequency	Total daily dosage
Uncomplicated	1 g	Every 8 hours (occasionally every 6 hours)	3 g (4 g)
Moderately severe or severe	2 g	Every 8 hours (occasionally every 6 hours)	6 g (8 g)
Infections generally needing antibiotics in higher dosage	3 g (2 g)	Every 6 hours (Every 4 hours)	12 g

Maintenance dosage of 'Mefoxin' in adults with reduced renal function

Renal function	Creatinine clearance (ml/min)	Dose	Frequency
Mild impairment	50-30	1-2 g	Every 8-12 hours
Moderate impairment	29-10	1-2 g	Every 12-24 hours
Severe impairment	9-5	0.5-1 g	Every 12-24 hours
Essentially no function	<5	0.5-1 g	Every 24-48 hours

In the patients undergoing haemodialysis, the loading dose of 1 to 2 g should be given after each haemodialysis, and the maintenance dose should be given as indicated in the table above.

Intravenous administration: reconstitute 'Mefoxin' with Water for Injection BP. 1 g is soluble in 2 ml. Although 'Mefoxin' is very soluble, for intravenous use it is preferable to add 10 ml of Water for Injection BP to the 1 g vial or the 2 g vial. Shake to dissolve and then withdraw entire contents of vial into syringe.

For direct intravenous injection, 'Mefoxin' may be slowly injected into

Outstanding clinical benefits

ide-ranging activity against Gram-negative and Gram-positive athogens, anaerobes as well as aerobes.

nusually high resistance to β-lactamase degradation.

ghly active against *Bacteroides fragilis* and strains of *E.coli*, erratia, Klebsiella spp. and Proteus spp. (including indole positive rains) resistant to other antibacterial agents.

ffers high levels of active antibiotic in the body.

record of relative safety comparable to the penicillins.

Prime indications include:

Peritonitis, and other intra-abdominal and intrapelvic infections.
Female genital tract infections
Septicaemia
Skin and soft tissue infections
Bone and joint infections
Urinary tract infections
Respiratory tract infections (e.g. inhalation pneumonia)

Specific clinical profile

efoxin is exceptionally valuable wherever Gram-negative pathogens d anaerobes are involved in mixed infections. When mixed fections are suspected, therapy may be started while awaiting the sults of susceptibility testing.

Mefoxin®

Cefoxitin sodium, MSD

INJECTION

First of the cephamycins

ein over a period of 3 to 5 minutes or may be given through the ng when the patient is receiving parenteral solutions.

ntermittent intravenous infusion of 'Mefoxin' may be employed n large amounts of fluid are to be given. However, during sion of the solution containing 'Mefoxin' it may be advisable porarily to discontinue administration of any other infusion tion at the same site (by using an appropriate IV infusion set).

olution of 'Mefoxin' may also be given by continuous intravenous sion (see below for compatibility and stability).

muscular administration ONLY

onstitute 'Mefoxin' 1 g with 2 ml of Water for Injection BP or % or 1% lignocaine hydrochloride (without adrenaline) solution oxin' is given by deep injection into a large muscle mass d injection into a blood vessel.

patibility and stability

olution of 'Mefoxin' in Water for Injection BP may be added to the wing solutions: 0.9% Sodium Chloride Injection BP, 5% or 10% trose Injection BP, Dextrose and Sodium Chloride Injection (0.9%, 5%, 0.45% or 4.3%, 0.18%), Lactated Ringer's Injection, 5% Dextrose in Lactated Ringer's Injection, 5% or 10% invert ar in water, 10% invert sugar in saline solution, 4.2% Sodium rbonate Injection BP, M/6 Sodium Lactate Injection BP.

oxin', as constituted to 1 g/10 ml with Water for Injection BP, er for Injection BP preserved with parabens or benzyl alcohol, Sodium Chloride Injection BP or 5% Dextrose Injection BP, tains satisfactory potency for 24 hours at room temperature, for ours under refrigeration, and for 13 weeks in the frozen state.

oxin' can be administered concomitantly with such antibiotics as amicin, tobramycin, carbenicillin or amikacin. When 'Mefoxin' is nistered with another antibiotic, they should not be mixed in the e syringe.

ra-indications

oxin' is contra-indicated in persons who have shown sensitivity to cefoxitin. In the absence of clinical experience, oxin' should not be administered to patients who have shown sensitivity to cephalosporins.

Precautions

There is some clinical and laboratory evidence of partial cross-allergenicity between cephamycins and other β-lactam antibiotics, penicillins and cephalosporins. Severe reactions (including anaphylaxis) have been reported with most β-lactam antibiotics.

Before therapy with 'Mefoxin', careful inquiry should be made concerning previous hypersensitivity reactions to β-lactam antibiotics. 'Mefoxin' should be given cautiously to penicillin-allergic patients.

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously. If an allergic reaction to 'Mefoxin' occurs, the drug should be discontinued.

The total daily dosage should be reduced when 'Mefoxin' is administered to patients with transient or persistent reduction of urinary output due to renal insufficiency (see 'Dosage and administration') because high and prolonged serum antibiotic concentrations can occur from usual doses.

Interference with laboratory tests

A false-positive reaction to glucose in the urine may occur with reducing substances but not with the use of specific glucose oxidase methods.

Use in pregnancy

Use of the drug in women of childbearing potential requires that the anticipated benefits be weighed against possible hazards. Reproductive and teratogenic studies have been performed in mice and rats and have revealed no evidence of impaired fertility or harm to the foetus due to 'Mefoxin'. There are no controlled studies with 'Mefoxin' in pregnant women.

Nursing mothers

'Mefoxin' is excreted in human milk.

Infants and children

Pending the outcome of clinical trials in progress, the conditions for use of 'Mefoxin' in infants and children remain to be defined.

Side effects

'Mefoxin' is generally well tolerated. Side effects rarely require stopping treatment and usually have been mild and transient.

Local reactions

Thrombophlebitis has occurred with intravenous administration. Pain, induration and tenderness after intramuscular injections have been reported.

Allergic

Maculopapular rash, urticaria, pruritus, eosinophilia, fever and other allergic reactions have been noted rarely.

Gastro-intestinal

Diarrhoea has been reported rarely.

Blood

Transient leucopenia and neutropenia have been reported. Some individuals, particularly those with azotaemia, may develop positive direct Coombs tests during therapy with 'Mefoxin'.

Liver function

Transient elevations in SGOT, SGPT, serum LDH and serum alkaline phosphatase have been reported rarely.

Kidney

Elevations in serum creatinine and/or blood urea levels have been observed. The role of 'Mefoxin' in changes in renal function tests is difficult to assess, since factors predisposing to pre-renal azotaemia or to impaired renal function usually have been present.

Presentation

In vials containing 1 g or 2 g of cefoxitin as the sodium salt. Each gram of cefoxitin contains approximately 51.5 mg (2.2 mEq) sodium.

Product licence numbers: 1 g 0025/0130; 2 g 0025/0131.

Product authorisation numbers: 1 g PA 35/42/1; 2 g PA 35/42/2.

Issued October 1978.

Additional information is available to the medical profession on request.

Basic NHS cost [illegible] for the 1 g vial and [illegible] for the 2 g vial.

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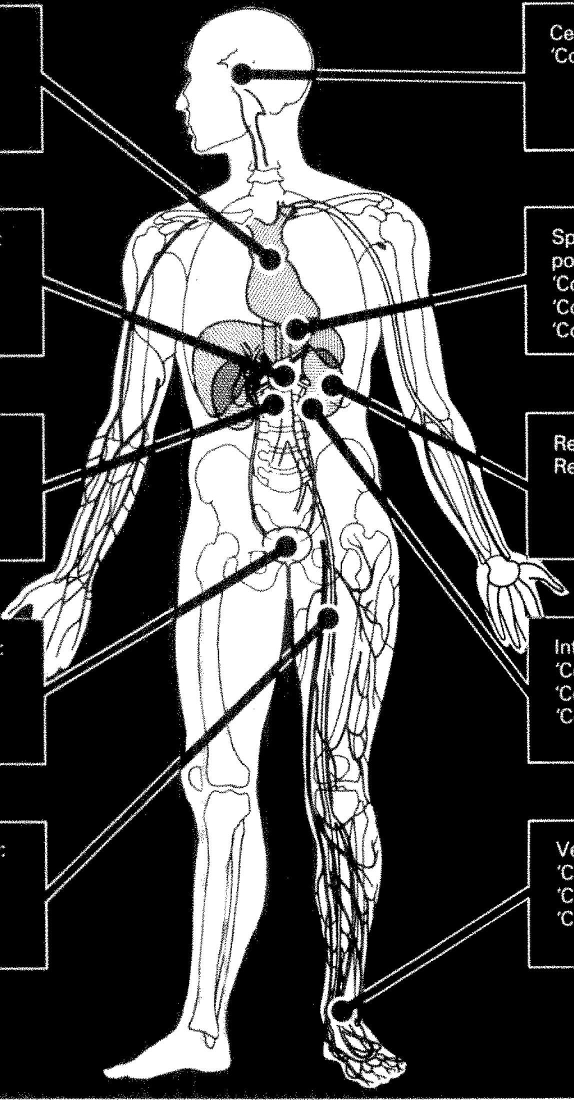

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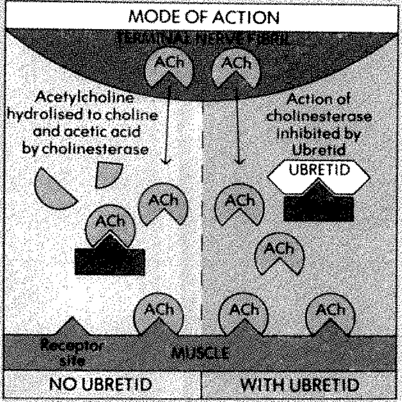
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Ref. Cameron, M.D. (1966), *J. Obstet. Gynaec. Brit. Cwlth.*, **73**, 847

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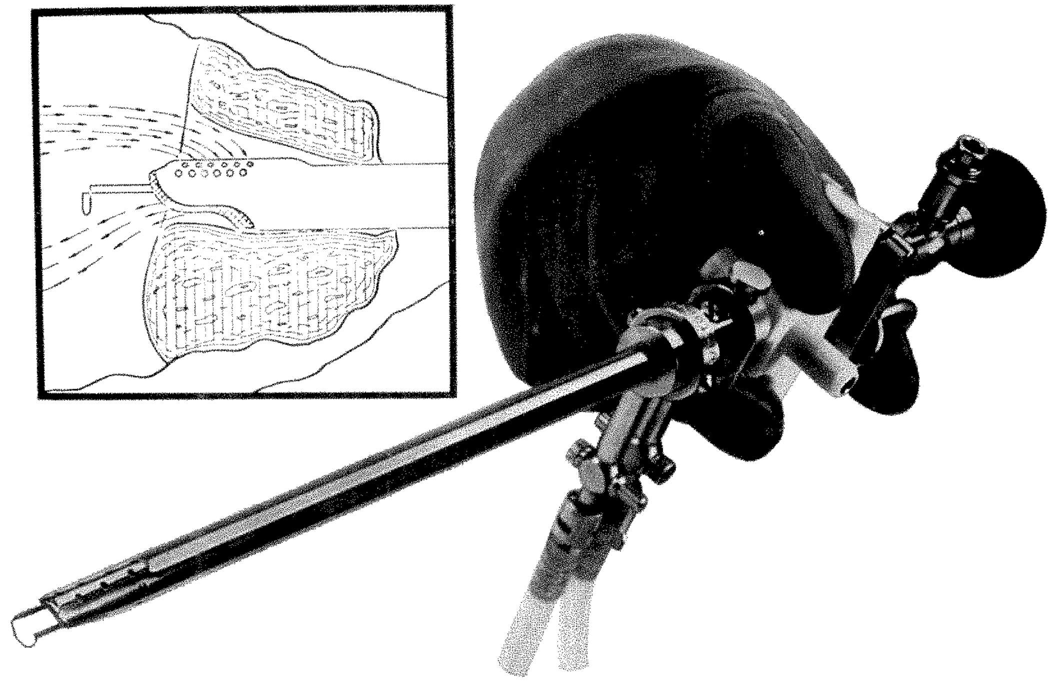

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The Diagnosis and Treatment of P.A.U.

Post-menopausal Atrophic Urethritis

Older women presenting with frequency, urgency and painful micturition often describe their condition as 'cystitis'. There can hardly be a woman in existence who has not suffered the transient discomfort of a 'simple cystitis' at some time in her early life, but as she reaches middle age, although the symptoms may appear to her as the same, the cause, particularly in the absence of infection, may be atrophic changes in the distal urethra responding to hormonal disparities of the menopause.[1]

Untreated, these atrophic changes can be devastating and demoralising in their effect.[2]

A delicate monitor of oestrogen activity, the distal urethra will deteriorate rapidly when deprived of the oestrogen to which it has become accustomed during the patient's fertile years. In the end the urethra will become stenosed.

Treating P.A.U. with Premarin*

Treatment with Premarin 0.625mg tablets can effect a rapid and complete elimination of symptoms.[3]

1. Oestrogen deprivation can be confirmed by vaginal cytology or assumed in the presence of vaginal atrophy or dryness, or other symptoms of oestrogen lack.
2. Low-dose Premarin (0.625mg) administered cyclically – 21 days on, 7 days off – for 3 months. Urethral epithelium is remarkably sensitive to oestrogens and so will respond to this low dose.
3. Frank urinary tract infection should of course be treated with appropriate antibiotics or urinary anti-infectives.
4. If treatment is instigated in the early stages of this disorder – for instance within the first six/twelve months of symptoms – it may be possible to reverse all symptoms of P.A.U. with Premarin alone!

However in patients with a longer history of frequency and urgency, if oestrogen therapy does not effect a rapid and complete elimination of symptoms then the possibility of a secondary urethral stenosis should be considered.

References:
1. Willington, F. L. The Practitioner 220, 739, 1978.
2. Smith, P. J. B., Ayerst Medical Library Vol. 2, No 2, 1978.
3. Smith, P. J. B., The Practitioner, 218, 97, 1977.

PREMARIN

(conjugated oestrogens)

Premarin tablets

Uses

Menopausal and post-menopausal oestrogen replacement therapy and allied disorders such as post-menopausal osteoporosis, atrophic vaginitis and post-menopausal atrophic urethritis.

Dosage and Administration

Menopausal and post-menopausal oestrogen deficiency: Premarin 0.625–1.25mg daily is the usual starting dose. Cyclic administration is recommended (three weeks' dosage followed by one week's rest). For maintenance, the lowest effective dose should be used. It is recommended that a physical examination, including endometrial assessment, wherever possible be performed at the time of the initial examination, and the endometrium assessed regularly thereafter at 6–12 month intervals. Break through bleeding is an indication for further investigation.

Contra-Indications: Uterine myomatosis. Endometriosis. Cancer of the breast and uterus. Active hepatic, renal and severe cardiac disease. Undiagnosed genital bleeding. Diabetes. Thyrotoxicosis. Pregnancy. Personal history of thrombosis.

Precautions

In the female – prolonged use of unopposed oestrogen may increase the risk of endometrial carcinoma.

Side Effects

Premarin is unlikely to cause gastro-intestinal symptoms, headaches, breast tenderness, salt and water retention which can occur with other forms of oestrogen therapy.

Product licence numbers

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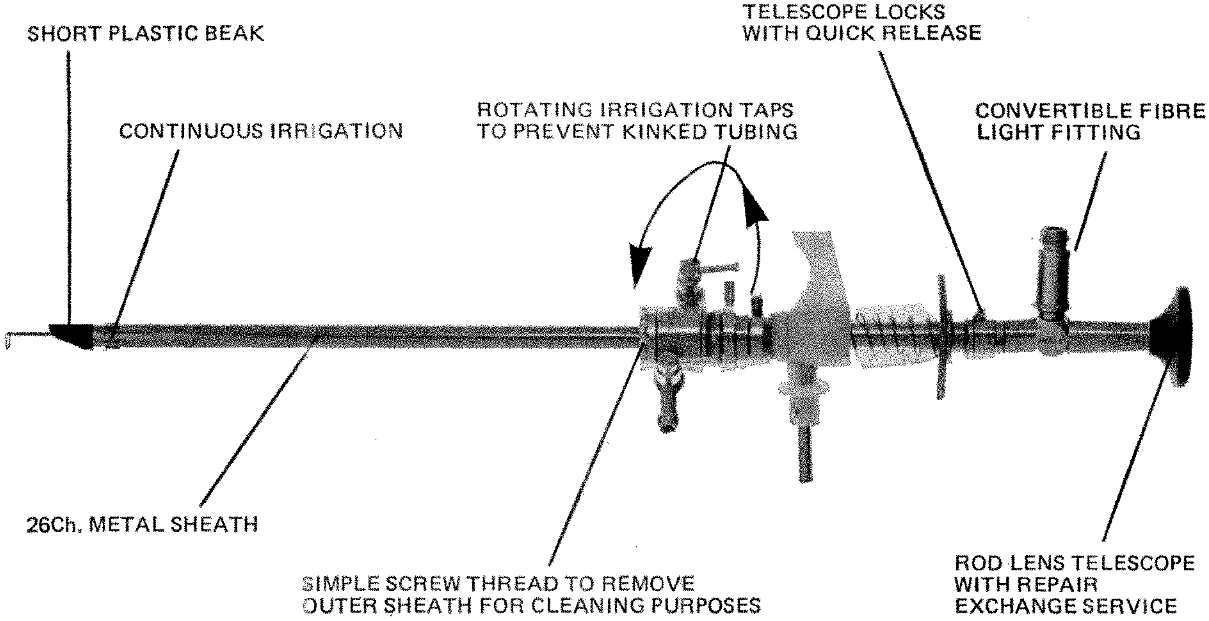

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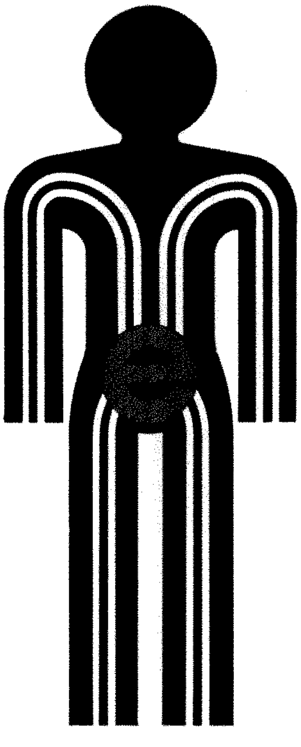

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With a unique action

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With unique results

In oestrogen-resistant carcinoma of the prostate, published results of treatment of over 500 patients with Estracyt relate to 80% with Stage IV disease and 20% Stage III. They show that SUBJECTIVE response to treatment, seen in 40% to 65% of oestrogen-resistant patients,[1,2] usually occurs within 14 days, relief of pain being the most obvious benefit. OBJECTIVE responses were seen in 19%–48% of patients with advanced disease.[3,4]

References

1. Nagel, R. and Kolln, C-P.: Treatment of Advanced Carcinoma of the Prostate with Estramustine Phosphate (1977). Brit. J. Urol., **49**, 73-79.
2. Mayer, E. J.: Orale Estracyt-Behandlung beim Prostatakarzinoma (1975) Ther. Umschau, **32**, 114-119.
3. Jonsson, G., Hogberg, B. and Nilsson, T.: Treatment of Advanced Prostatic Carcinoma with Estramustine Phosphate (Estracyt) (1977). Scand. J. Urol. Nephrol., **11** (In press).
4. Mittleman, A., Shukla, S. K. and Murphy, G. P.: Extended Therapy of Stage D Carcinoma of the Prostate with Oral Estracyt (1976). J. Urol., **115**, 409-412.

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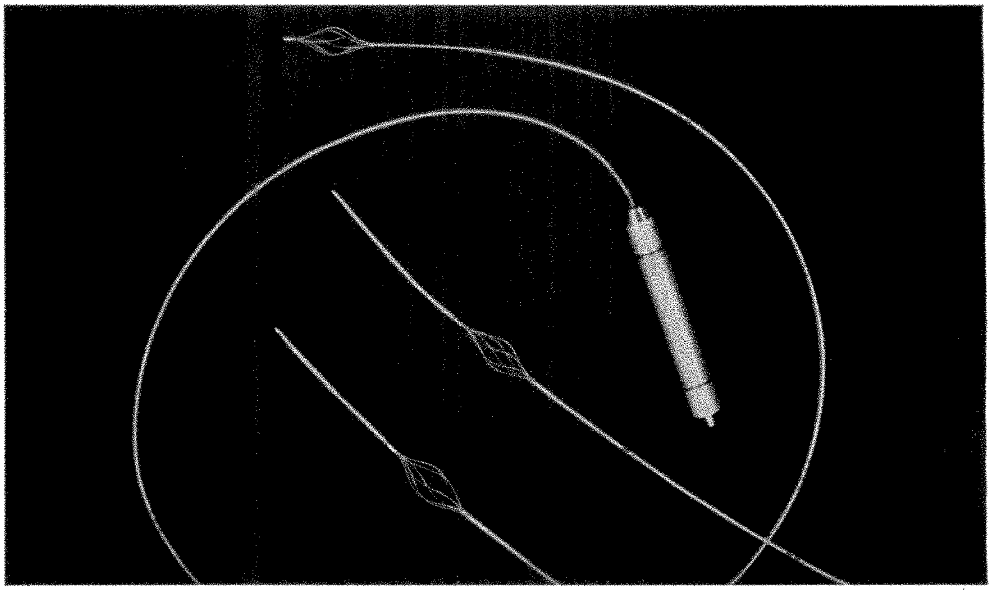

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British Journal of Urology (1978), **50**, 433-436

The Distinction between Obstructive Uropathy and Nephropathy by Radioisotope Transit Times

H. N. WHITFIELD, K. E. BRITTON, W. F. HENDRY, C. C. NIMMON and J. E. A. WICKHAM

Departments of Urology and Nuclear Medicine, St Bartholomew's Hospital, London

Summary—Deconvolution analysis of different regions of interest on gamma camera renography enables obstructive lesions causing impairment of nephron function to be distinguished from obstructive lesions in which parenchymal function is unimpaired. Quantitation of isotope transit time through the parenchyma is a reliable method of diagnosing upper urinary tract obstruction.

The diagnosis of obstruction as a cause of upper urinary tract dilatation may be made radiologically or urodynamically. In a previous study we have shown that the results of pressure/flow studies correlate well with the percentage increase in the size of the renal pelvis after a diuretic during high dose intravenous urography (Whitfield *et al.*, 1977).

Gamma camera renography may also be employed to study obstructive lesions. This technique has the advantage that differential renal function can be estimated and isotope transit through different regions of the kidney can be compared. Deconvolution analysis of the gamma camera renogram enables the retention functions to be obtained from which the isotope transit times through defined regions of interest are quantitated.

We proposed that isotope transit times through the parenchyma could be used as a means of determining whether an obstructive uropathy was affecting nephron function and thus causing an obstructive nephropathy (Whitfield *et al.*, 1977). This hypothesis could be tested by long-term follow-up of patients to assess whether the outcome predicted on the basis of gamma camera information was fulfilled.

This paper reports the renographic results in 22 patients who were suspected of having some degree of upper urinary tract obstruction. All have been followed by serial renography whether or not surgery was undertaken.

Patients and Methods

Twenty-two patients, 10 males and 12 females, whose ages ranged from 8 to 55 years were included in the study. A significant degree of pelviureteric junction obstruction was diagnosed clinically and by the finding of a dilated renal pelvis on conventional urography. The results of diuretic urography, urodynamic studies and gamma camera renography were noted but did not always influence the decision about surgery.

Radioisotope transit times through the kidney are measured as follows. The patient is hydrated normally and studied seated with a scintillation detector set over the region of the heart and the gamma camera viewing the back. The patient receives 10 to 15 mCi ^{99m}Tc-DTPA intravenously and the gamma camera data are recorded for 20 to 30 min using an on-line Varian 620/L 100 computer. The data are displayed not only conventionally as the variation in the distribution of count rates with time but also as a "functional" image of the distribution of mean times. This mean time image highlights the late arrival of activity in the renal pelvis and makes the setting up of a region of interest over the pelvis much easier. Regions of interest are also set up over the whole of both kidneys from an image formed at 2 min. From these regions of interest the radioisotope activity/time curves are obtained. The renal parenchymal curve is derived by subtracting the pelvic curve from the whole kidney curve. Using the renal input obtained from the detector over the heart and each parenchymal and whole kidney activity/time curve in turn, deconvolution analyses are performed. These give the retention of activity with time that would have resulted from a theoretical spike injec-

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Read at the 34th Annual Meeting of the British Association of Urological Surgeons in Brighton, June 1978.

tion into a renal artery. These retention functions are corrected for the effects of non-renal activity and non-extracted tracer. The area under the retention function divided by its height is a measure of the mean renal radioisotope transit time of either parenchyma or whole kidney depending on the region selected. Since renal transit times are affected by urine flow, the shortest transit time is subtracted from the mean transit time of the parenchyma to correct for this effect. This accounts for the change from our previously published upper limit of normal of 115 parenchymal transit time units (Ap units) to 72 Ap units (Whitfield *et al.*, 1977).

In the patient with a dilated renal pelvis radiologically the absence of obstructed nephropathy is demonstrated by the fact that the parenchymal transit time remains normal although the whole kidney (parenchyma plus pelvis) transit time is increased (Fig. 1). With an obstructive uropathy causing obstructive nephropathy both whole kidney and parenchymal transit times are increased (Fig. 1). This is because there is relatively increased salt and water retention associated with the presence of an obstructive nephropathy which prolongs the intratubular luminal transit of a non-reabsorbable solute such as 99^mTc-DTPA. These findings allow one to distinguish whether or not an obstructive nephropathy is present when there is dilatation of a renal pelvis radiologically.

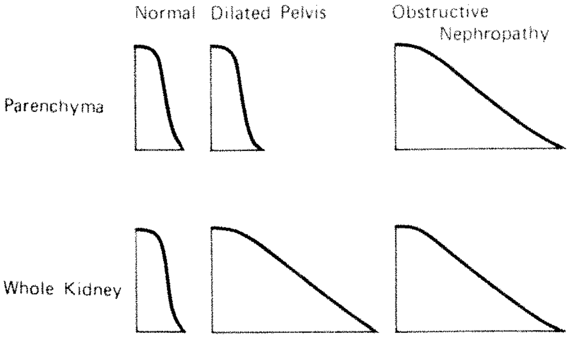

Fig. 1 Radioisotope retention functions. Whole kidney and parenchymal retention functions of a normal kidney, a kidney with a dilated renal pelvis which is unobstructed and a kidney with a dilated pelvis which is obstructed.

Sixteen of the 22 cases underwent pyeloplasties, 15 by the Anderson Hynes technique and one patient had a Culp pyeloplasty.

Results

Operative Group (16 cases) (Fig. 2)

In these 16 cases quantitative gamma camera information is missing pre-operatively in 2 and post-operatively in 1, because of computer failure at the time of renography: so 13 cases who were thought to be significantly obstructed are available for study.

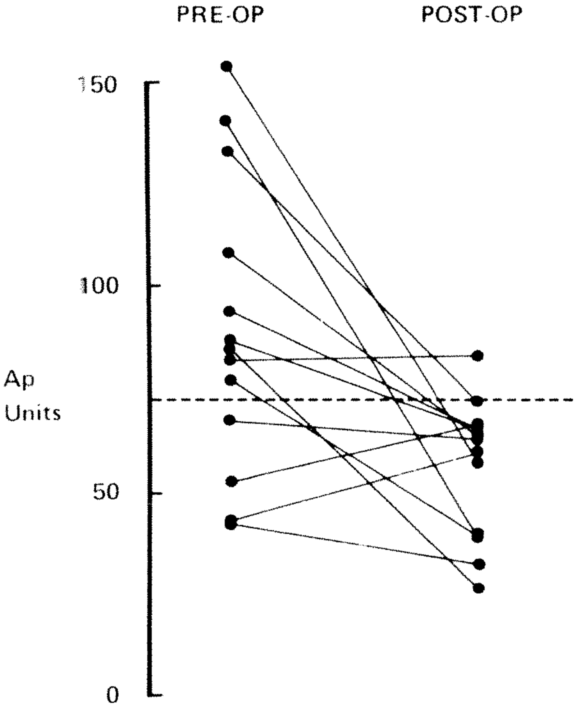

Fig. 2 Pre-operative and post-operative retention functions in the operated group.

Nine cases were renographically obstructed pre-operatively. In 8 of these parenchymal transit times returned to normal post-operatively; in all 8 there is no longer radiological evidence of obstruction and the patients are symptom free. The ninth case remains radiographically obstructed, continues to have symptoms and is awaiting re-operation.

Four cases who were renographically unobstructed underwent surgery and all remain renographically unobstructed after surgery. Two patients with dilated renal pelves (Ap values 43 and 52) were unobstructed urodynamically and on diuretic urography; in one of these patients removal of a twisted ovarian cyst subsequently cured her symptoms. One patient (Ap value 68) had a very short history but was unequivocally obstructed on radiological and urodynamic evidence. The fourth patient (Ap value 41) was urodynamically unobstructed and radiologically borderline and still has pain post-operatively which is presumed to be non-renal in origin.

Non-operated Group (6 cases) (Fig. 3)

Of the 6 cases who did not undergo surgery 4 were renographically unobstructed. Two of these cases were radiologically unobstructed but urodynamically equivocal, one was radiologically borderline and urodynamically equivocal and one was both radiologically and urodynamically unobstructed. In all 4 cases not only has parenchymal transit time remained within normal limits but differential renal function is unaltered.

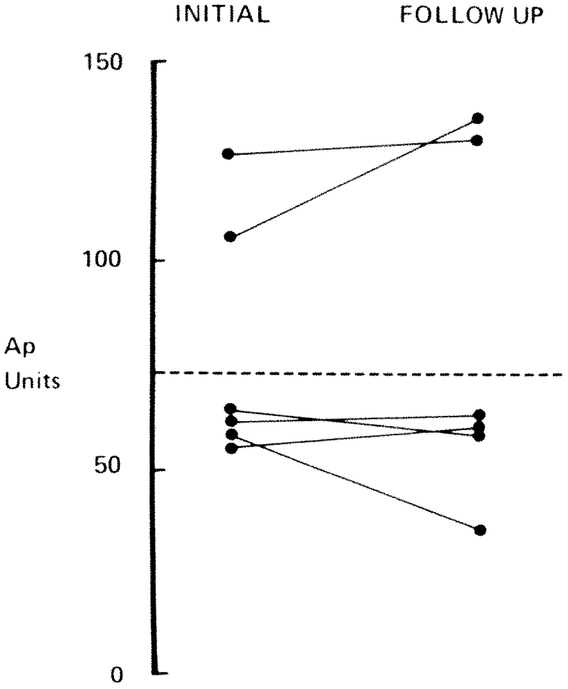

Fig. 3 Initial and follow-up retention functions in the non-operated group.

Two cases who were renographically obstructed did not undergo surgery. Both were radiologically and urodynamically unobstructed. In one case differential renal function has fallen from 35% to 15% but radiologically there is no evidence of obstruction. In the other case differential renal function has fallen from 50% to 35% and radiological evidence of obstruction is now present.

Discussion

Conventional probe renography has been considered unreliable as a method of diagnosing upper urinary tract obstruction since it was realised that it was not possible to distinguish a capacious collecting system from a truly obstructed one. Gamma camera images bring a new dimension to renography and enable the handling of isotope by the parenchyma to be separated from the passage of isotope through the collecting system. An estimate of nephron function in terms of isotope handling can thus be obtained.

Deconvolution analysis is a mathematical way of deriving from intravenous renographic information the way in which a kidney would handle a single intra-arterial bolus injection of isotope. The validity of this technique has been proven experimentally (Price *et al.*, 1978). Deconvolution analysis can be applied to probe renography (Britton and Brown, 1971). Only with a gamma camera renogram, however, can parenchymal isotope handling be separated from that of the collecting system.

These results show that quantitation of the gamma camera renogram by deconvolution analysis is a reliable method of diagnosing upper urinary tract obstruction. By providing information about the effects of obstruction on parenchymal isotope transit times an indication of obstructive nephropathy can be obtained in addition to evidence of obstructive uropathy which can also be diagnosed by other methods. Additional information about differential renal function is invaluable and the low radiation dose when compared to intravenous urography makes it the most suitable investigation for serial long-term follow-up studies.

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An Assessment of Computerised Isotopic Renal Section Scanning

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Summary—The basic non-invasive investigation of renal space occupying lesions by excretion pyelography was coupled with ultrasonic scanning.

Forty-one patients who have undergone isotopic section scanning as part of their investigative assessment were studied.

The conditions investigated included solitary cysts, polycystic kidneys, renal tumours, tumefactive xanthomatous pyelonephritis, renal infarct and non-functioning kidneys. An analysis of the accuracy of isotopic section scanning in these different pathological states was made.

Computerised isotopic section renal scanning offers a new non-invasive renal investigative technique.

The main non-invasive radiological or para-radiological methods of investigating the renal tract are high quality intravenous pyelography and ultrasonic scanning.

Computerised isotopic renal section scanning (MacDonald *et al.*, 1977) represents an additional non-invasive renal investigative technique. It measures and displays radio isotope uptake in the kidneys, thereby showing anatomy and function. It depends on the use of a radio-pharmaceutical which is taken up by the kidney, with a high organ to background ratio, and retained by renal tissue sufficiently long for adequate scanning examinations to be carried out. It should not be excreted rapidly enough for the pelvicaliceal content to complicate the picture.

Dimercaptosuccinic acid (DMSA) labelled with technetium was used (Arnold *et al.*, 1975; Handmaker *et al.*, 1975). This is a metal chelate which attaches to plasma protein, and 60% is taken up by the kidneys and concentrated in the parenchyma with a cortex to medulla ratio of 17:1, thereby giving good cortical definition. Only about 10% is excreted in the urine in the first 2 hours.

Patients and Methods

Forty-one patients undergoing renal investigation were studied. There were 26 men and 15 women and the age range was 20 years to 83 years. An intravenous pyelogram and isotopic section scan were done on all the patients. Most patients, in particular those with space occupying lesions, also had an ultrasonic scan performed. Where indicated arteriography was carried out.

Scanning was performed on the Aberdeen Section Scanner, a dual detector radio-isotope scanner with the facility to rotate through 180°. This equipment enables transverse section emission gamma ray imaging, which is analogous to the EMI type of X-ray scanner (Kuhl and Edwards, 1964).

Each patient received 2mCi of technetium-labelled DMSA intravenously and was scanned up to 2 h later; the estimated kidney dose was 2.8 rad. Conventional anterior and posterior images took up to 25 min to perform; a further 15 min were spent on a transverse section at an appropriate level. The 2 detectors made a single pass across the patient so that a count density profile was obtained. The 2 detectors were then rotated about the patient through a 6° angle and another scan pass performed, and so on. A total of 30 such profiles constituted the basic data which were correlated in a small digital computer to produce the section image (Fig. 1).

This technique was similar in principle and computer programming to the transverse computer-assisted tomographic apparatus developed by EMI (Ambrose, 1973). Whereas the EMI X-ray tech-

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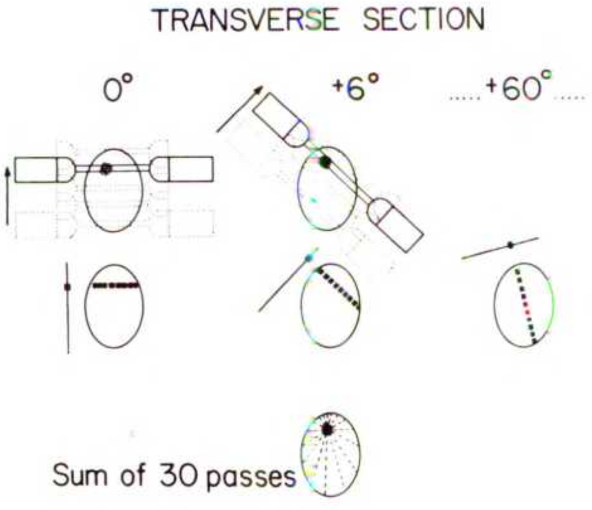

Fig. 1 The technique of renal section scanning.

nique demonstrates anatomy and pathology, the isotope method principally demonstrates anatomy and function.

Results

The normal DMSA renal scan showed, fairly accurately, the shape, size and position of the renal substance on each side. The anterior scan of the right kidney was somewhat complicated by the overlying liver which unfortunately accepts some of the DMSA, but it was usually better defined on the posterior scan. The tomographic section through the middle of the kidney showed a smooth ovoid organ with maximal activity in the cortex and therefore an apparent gap in the centre, which was made up of medulla and the collecting system (Fig. 2).

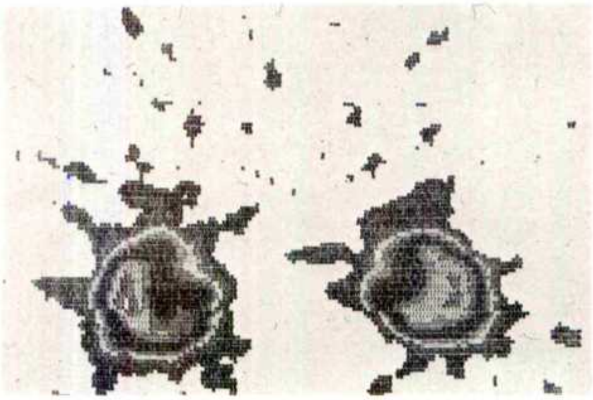

Fig. 2 Normal renal section scan. The left kidney is on the right.

The 41 patients were divided into 4 groups:

(1)	"Normal"	11 patients
(2)	Cysts	10 patients
(3)	Tumours	14 patients
(4)	Miscellaneous	6 patients.

"Normal"

There were 11 patients in this group consisting of 7 men and 4 women aged between 38 and 77 years (Table 1). In 6 patients an excretion urogram had raised doubt about a possible space occupying lesion (SOL), 3 patients had hypertension and 2 patients had renal pain and splenic calcification respectively. In 10 of the 11 patients the renal isotope section scan was negative. In the eleventh patient there was a suggestion of a renal mass involving the anterior surface of the right kidney which on further investigation by arteriography and ultimately post-mortem examination was

Table 1 The Findings in Patients with "Normal" Kidneys

Sex	*Age*	*IVP*	*Ultrasonic Scan*	*Isotopic Scan*	*Arteriogram*	*Pathology*
M	50	? SOL	NAD	NAD	–	Haematuria
M	77	? SOL	NAD	NAD	–	Myeloma
F	50	? SOL	–	NAD	–	Multiple Sclerosis
M	53	? SOL	NAD	NAD	–	Pyrexia of Unknown Origin
M	39	? SOL	Spleen	NAD	–	Porphyria
F	68	? SOL	Liver Mass	Rt Renal Mass	NAD	2° T Liver
F	45	NAD	–	NAD	–	Hypertension
M	38	NAD	–	NAD	–	Hypertension
M	46	NAD	–	NAD	–	Hypertension
F	66	NAD	NAD	NAD	NAD	Splenic Calcification
M	48	NAD	–	NAD	–	Renal Pain

found to be due to a secondary tumour in the overlying liver. This case illustrated one of the major difficulties in interpretation of lesions of the anterior aspect of the right kidney.

Cysts

In this group there were 10 patients, 5 men and 5 women, ranging in age between 26 and 72 years (Table 2). Eight had simple cysts, one patient had multiple cysts and one patient polycystic kidney.

On transverse section scan a cut through the cyst showed no activity, a cut through the normal renal tissue showed normal renal outline but a cut through the margin of the cyst and kidney confirmed the sharp delineation of the lesion (Fig. 3).

Similar sharp delineation of the lesion was seen in polycystic kidneys and in addition the actively functioning portions of the renal parenchyma were demonstrated (Fig. 4).

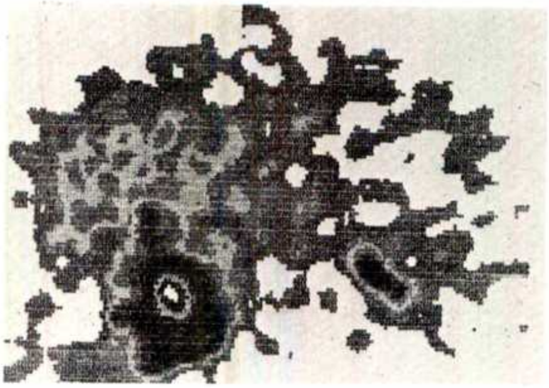

Fig. 4 Section scan showing bilateral polycystic kidneys: note the poor function of the left kidney, and increased liver uptake because of poor renal function.

Table 2 The Findings in Patients with Renal Cysts

Sex	*Age*	*IVP*	*Ultrasonic Scan*	*Isotopic Scan*
M	57	SOL	Cyst	Cyst
M	71	Cyst	Cyst	Cyst
F	62	Multiple Cysts	–	Multiple Cysts
F	67	Cyst	Cyst	Cyst
M	44	Cyst	Cyst	Cyst
F	43	Cyst	Cyst	Cyst
F	50	Polycystic	Polycystic	Polycystic
M	60	Cyst	Cyst	Cyst
M	72	Cyst	Cyst	Cyst
F	26	Cyst	Cyst	Cyst

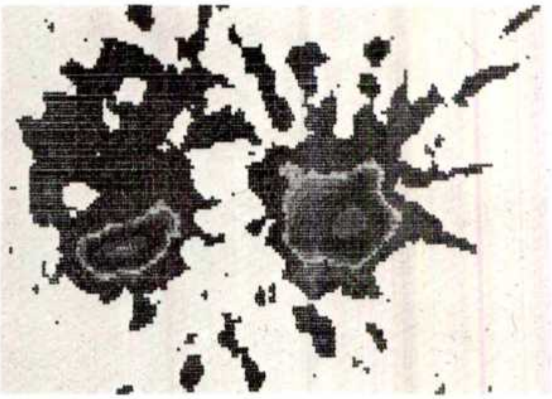

Fig. 3 Section scan showing a cyst of the right kidney: note the sharp delineation of the cyst.

Tumours

This group consisted of 9 men and 5 women ranging in age from 48 years to 76 years (Table 3). In transverse section scanning there was a poorly defined margin between the normal renal tissue and the primary renal tumour (Fig. 5). Problems arose in differentiating between cyst and tumour, cystic tumours, avascular tumours and tumours undergoing necrosis. Of the 14 patients with tumour in this series there was no difficulty in identification in 9, but in the remaining 6 patients isotopic section scan suggested that the lesion was probably a cyst. In 2 this was found to be because the lesion was a cystic tumour, in one patient there was an associated renal cyst nearby, and in the fourth patient the lesion was an avascular tumour. In the final 2 patients necrosis in a tumour confused the diagnosis.

Miscellaneous

There were 6 patients in this group, 5 men and one woman ranging in age from 20 years to 83 years (Table 4). Four patients had a non-functioning kidney, one had an associated staghorn calculus, one a possible space occupying lesion of the kidney and the sixth patient had an infarct of the lower

Table 3 The Findings in Patients with Renal Tumours

Sex	*Age*	*IVP*	*Ultrasonic Scan*	*Isotopic Scan*	*Arteriogram*	*Pathology*
F	70	T	–	T	–	T
M	69	T	–	T	–	T
M	52	T	T	C	T	T
M	68	T	T	C	T	T
M	53	T	T	T	–	T
F	76	T	T & C	Multiple Cysts	T & C	T & C
M	48	T	T	T	T	T
M	51	SOL	T	C	Avascular Tumour	T
M	68	T	T	T	–	T
F	52	SOL	T	C	T	Cystic T
F	60	T	–	T	T	T
M	65	T	T	T	–	T
F	65	T	Cystic T	C	–	Cystic T
M	69	T	T	T	T	2° T

(C = Cyst T = Tumour)

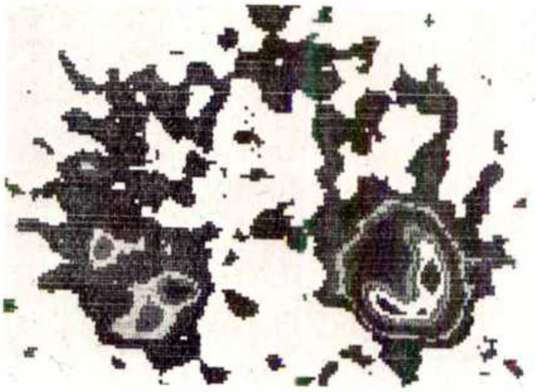

Fig. 5 Section scan showing a tumour of the right kidney: note the ill-defined delineation.

pole of the kidney. In 3 of the 4 patients with non-functioning kidneys the isotope section scan failed to show any activity in the kidney, and in the fourth patient it showed up a small atrophic kidney as the cause of non-function. In one of the non-functioning kidneys an ultrasonic scan had suggested the possibility of a tumour because of expansion of the renal mass which was in fact due to a perinephric abscess.

The patient in whom the intravenous pyelogram suggested a tumour was found, on ultrasonic scan, to have a solid expanded lesion of the kidney. The isotopic section scan showed diminished uptake not characteristic of either a cyst or tumour. Arteriography confirmed the diagnosis of tumefactive xanthomatous pyelonephritis. The final patient in this group had an infarcted lower pole of the kidney due to previous trauma. On isotopic renal scan this showed as an "abbreviated" kidney.

Discussion

In the normal group of patients the problem of a

Table 4 The Findings in Patients with Miscellaneous Lesions of the Kidney

Sex	*Age*	*IVP*	*Ultrasonic Scan*	*Isotopic Scan*	*Arteriogram*	*Pathology*
M	52	Non-Function	–	Rt Atrophic	–	Rt Atrophic
M	72	Non-Function	Cyst	Non-Function	–	Ureteric Tumour and Hydronephrosis
M	35	Non-Function	Nil	Nil	–	Hydronephrosis
F	61	Non-Function Staghorn Calc.	? Tumour	Non-Function	–	Perinephric Abscess
M	83	SOL	Tumour	Smaller Renal Area	Tumefactive Xanthomatous Pyelonephritis	–
M	20	Scarred Lower Pole	–	"Abbreviated" Kidney	Infarct Lower Pole	Old Trauma

hepatic mass overlying the anterior surface of the kidney causing misinterpretation was demonstrated. This pitfall should be remembered when dealing with anterior right renal masses.

In the group of patients with renal cysts the section scan was accurate in confirming the nature of the renal space occupying lesion.

The classical renal tumours were identified without difficulty but in those patients with cystic or avascular or necrotic lesions, the renal section scan was very similar to that of a simple cyst – *i.e.* a false negative. In this group of patients the ultrasonic scan was more accurate than the isotope section scan.

In severe inflammatory lesions of the kidney, such as perinephric abscess or tumefactive xanthomatous pyelonephritis, there was a marked destruction of functioning renal tissue despite an increase in the apparent renal size. With renal section scanning it was possible to indicate the discrepancy between the apparent size of the renal mass and its functional component, thereby facilitating a more accurate diagnosis. In the presence of a wholly non-functioning kidney the isotope section scan was of limited value.

It is concluded that isotopic renal section scanning can be of value in assisting in the delineation of renal lesions when combined with high quality excretion pyelography and ultrasonic scanning. If the limitations of isotope renal section scanning are accepted then this simple and non-invasive technique, combined with ultrasonic scanning, increases the accuracy of diagnosis in renal lesions and has a definite place in the investigation of the kidney.

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A New Urinary Test for Stone "Activity"

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Summary—Rapid evaporation of urine to osmolarity 1200 results in a high incidence of envelope Wedellite and calcium phosphate crystals. The Wedellite crystals closely resemble those seen in untreated urine samples of stone formers.

The incidence of crystalluria produced by these tests is higher in the stone formers than in the normal subjects, reduced by thiazides and increased by cellulose phosphate; combined thiazide and cellulose phosphate therapy was most effective in reducing crystalluria.

Simple calcium and oxalate concentration products were calculated and did not correlate well with incidence of calcium oxalate crystalluria. Although the product is important, inhibitors of crystal formation must be equally important.

It is postulated, but not proven, that the evaporation tests may indicate normal subjects at risk to stone formation when exposed to chronic dehydration and whether a stone former is still metabolically active.

One of the greatest problems in assessing the clinical status of a urinary stone former is to decide whether or not he is an active stone former at the time of evaluation. The fact that a patient has recently passed a stone gives no indication of when that stone was made. It could have been of very recent manufacture or alternatively it could have been made decades earlier when the urine composition was very different from those recently analysed.

There is therefore an urgent need for a test which will assess the tendency of a given urine sample to induce stone formation. Various attempts to devise such a test have been made but have been fraught with problems. Hallson and Rose (1976) studied urinary crystals at 37°C and found differences between random samples from normal subjects and from stone formers. However, stone formers are invariably advised to increase fluid intake, with the result that many urine samples are too dilute to show crystals even though they might have done so had fluid intake not been increased. Consequently, while the observation of crystals and crystal aggregation is of value, often no crystals are to be seen and testing is then of no particular value except to reveal that the urine sample is dilute. Our first attempt to overcome this problem was to add calcium and oxalate solutions to urine samples as others have done (Vermeulen *et al.*, 1964), but by means of motorised syringes and then to observe the crystals which resulted. It was thought that there might be a difference in the crystal types induced in normal subjects as opposed to stone formers. However, using this technique the calcium oxalate crystals formed did not resemble those seen in untreated urine. Instead there was a high incidence of branched crystals at slow rates of infusion and of amorphous crystals at high rates of infusion. This technique was therefore abandoned in favour of another approach which we believe has not been previously reported. The new technique was to observe all urine samples at a standard concentration by simply evaporating rapidly in a vacuum rotatory evaporator at 37°C to a urinary concentration of 1200 mmol/l and then to observe the crystals in the urine.

Patients and Methods

Urine samples were collected from normal subjects and from patients with urinary calcium oxalate/phosphate stones and with idiopathic hypercalciuria. The stone formers were usually attending a metabolic stone clinic held during the morning, and some were untreated or treated with diet only, and some were on either a thiazide diuretic and/or cellulose phosphate in order to lower urinary calcium. Samples of urine were passed directly into warmed vacuum flasks and quickly

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examined for crystals by warm stage microscope as previously described (Hallson and Rose, 1976). If crystals were not present then the osmolarity was measured by freezing point depression technique and the amount of water to be removed to yield a concentration of 1200 mmol/l was calculated. The sample, usually about 25 ml, was transferred to the rotatory evaporator and the water removed at 37°C. By collecting the distilled water into a measuring cylinder the volume of water removed from the urine could be continuously monitored and the procedure stopped at the appropriate time. Using this technique the rate of water removed was about 2 ml per min so that the time required for this step was quite brief. The concentrated urine was allowed to stand for 1 h, after which it was re-examined for crystals on the 37°C microscope stage (Fig. 1).

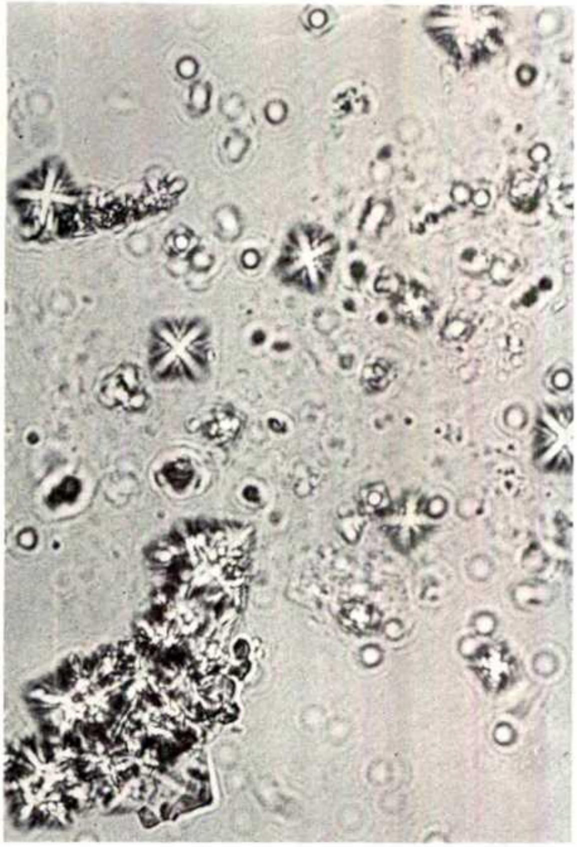


Fig. 1 Example of envelope Wedellite (calcium oxalate dihydrate) crystals induced by evaporating a urine sample of a stone former at pH 5.3. Red blood cells are also present and serve to indicate size of crystals. The large aggregate (lower left) is a mass of envelope crystals which cannot all be focused simultaneously.

Initially this test was performed only at the original pH of the urine, but in view of the high incidence of phosphate crystals observed at pH 6 and over, and in view of our special interest in oxalate crystals, later urine samples were split into 2 portions. One portion was brought to pH 5.3 before evaporation and the other portion was kept at the initial pH.

Urine samples were analysed for calcium by the flame atomic absorption method, oxalate by the enzymatic method of Hallson and Rose (1974) and phosphate by Coulter Kem-O-Lab discrete multi-channel analyser using the Fiske Subbarow method.

Results

The incidence of oxalate and phosphate crystals occurring at natural pH before and after evaporation in urine samples from normal subjects and from stone formers without and with treatment is shown in Figure 2. Similar data largely from the same urine samples but after adjustment of urine pH to 5.3 are shown in Figure 3. It can be seen that at natural pH the incidence of crystals in unevaporated urine samples was 16% in normal subjects and 27% in the stone formers, these values being rather similar to those previously reported (Hallson and Rose, 1976). However, after evaporation of those samples which did not show crystals previously, the total incidence of crystals rose to 49.5% and 87.5% respectively. The Table shows the mean calcium and oxalate concentrations and the product of the 2 concentrations in the various groups of urine samples. The relationship of the calcium and oxalate concentration product to the occurrence or absence of oxalate crystals is shown in Figure 4 and to the incidence of oxalate crystals in Figure 5.

In Figure 6 an attempt has been made to select a group of stone formers such that the mean and distribution of the calcium and oxalate concentration products match those of the normal controls. To do this the products from the normal controls were divided into 7 classes according to numerical value and the arithmetic mean of each class was found. The products for stone formers were also divided into the same 7 classes. Individual product values were then selected from each stone former's class in such a way as to give as near as possible the same arithmetic mean as in the corresponding normal control class. Similarly the number of individual products selected from each stone form-

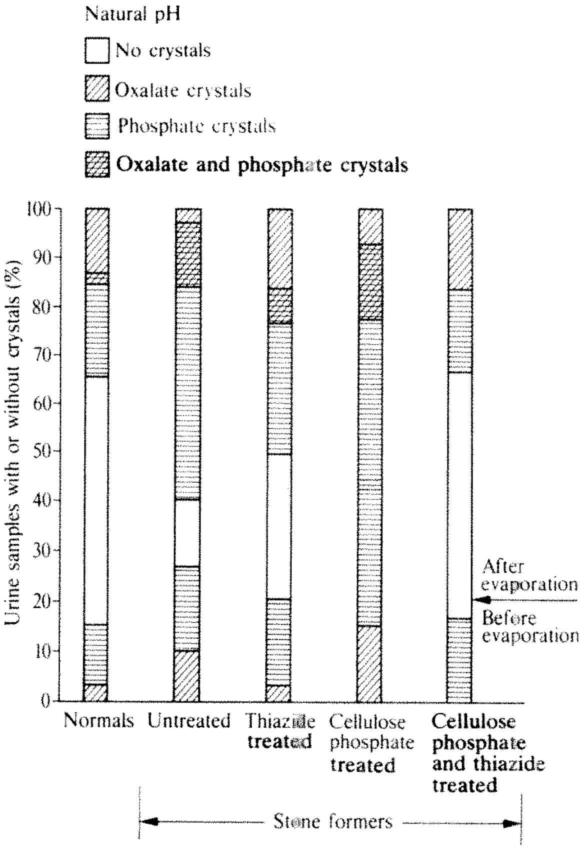


Fig. 2 Incidences of crystals in urine samples at natural pH before and after evaporation from normal subjects and stone formers with idiopathic hypercalciuria.

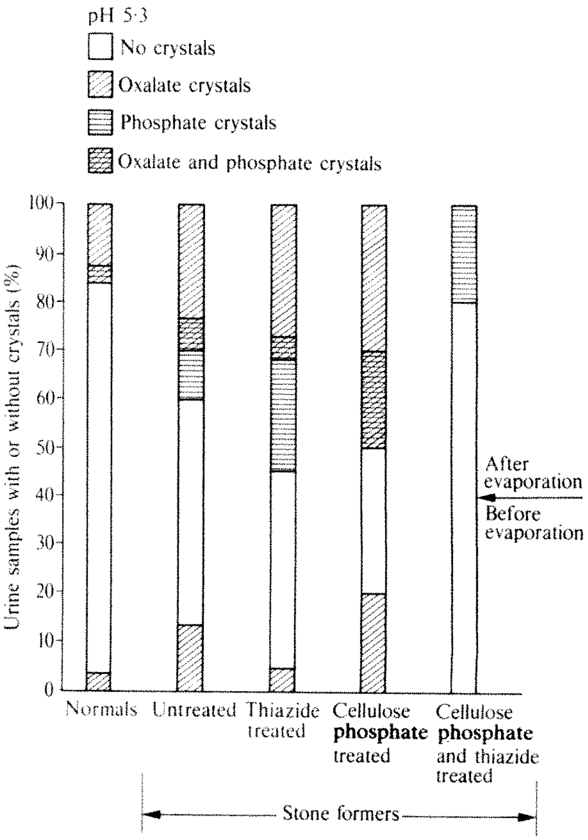


Fig. 3 Incidences of crystals in urine samples at pH 5.3 before and after evaporation from normal subjects and stone formers with idiopathic hypercalciuria.

ing class was arranged so that the overall frequency in the stone forming distribution matched the frequency in the normal class as far as possible. The selection was made "blind" with respect to the presence or absence of crystals in the individual samples. Out of 59 samples of stone formers, 26 were removed.

Discussion

It was encouraging to have found a technique which produced crystals in urine of a structure similar to those which occur naturally in urine. The example shown in Figure 1 reveals that the envelope type of calcium oxalate crystal, believed to be the dihydrate, can be produced both as single crystals and in aggregates as occur in stone formers (Robertson *et al.*, 1969). Such an encouraging finding is, however, not too surprising since the procedure of rapid evaporation at 37°C seems to be analagous to the concentration of urine in the renal tubules by water removal. It is therefore suggested that this rapid evaporation technique is preferable in studying crystal formation to techniques of addition of calcium and oxalate, since the latter give quite different crystal types.

It was hoped initially that a clear difference might emerge between urine samples of normal subjects on the one hand and stone formers on the other hand. However, such a hope is perhaps rather naive for various reasons. Firstly, the evaporation technique tests what would happen to the urines were the individuals to be subjected to conditions of dehydration and there could be amongst the normal group a number of individuals who would in fact become stone formers under such conditions. Secondly, it is not certain that all the untreated stone formers were still metabolically active and some of them might have been normal at the time of the test. Hence while the incidence of

Table Mean Calcium and Oxalate Concentrations and the Product of the 2 in Various Types of Urine Samples after Evaporation

Group	*pH*	*Type of crystal formed*	*[Ca] mmol/l*	*[Ox] mmol/l*	*[Ca] [Ox]*	*N*
Normals	Original	Oxalate	6.01	0.283	1.80	17
Normals	Original	None or phosphate only	5.32	0.299	1.58	65
Normals	5.3	Oxalate	6.19	0.297	1.86	14
Normals	5.3	None or phosphate only	5.46	0.285	1.56	81
Untreated stone formers	Original	Oxalate	7.43	0.230	1.80	7
Untreated stone formers	Original	None or phosphate only	6.66	0.321	2.15	25
Untreated stone formers	5.3	Oxalate	8.69	0.291	2.65	8
Untreated stone formers	5.3	None or phosphate only	7.52	0.307	2.36	18
Thiazide treated stone formers	Original	Oxalate	5.55	0.255	1.38	7
Thiazide treated stone formers	Original	None or phosphate only	5.77	0.304	1.66	16
Thiazide treated stone formers	5.3	Oxalate	6.36	0.225	1.43	7
Thiazide treated stone formers	5.3	None or phosphate only	5.74	0.282	1.55	13
Cellulose phosphate treated stone formers	Original	Oxalate	6.72	0.556	3.69	3
Cellulose phosphate treated stone formers	Original	None or phosphate only	5.66	0.422	2.13	7
Cellulose phosphate treated stone fromers	5.3	Oxalate	8.48	0.452	3.57	5
Cellulose phosphate treated stone formers	5.3	None or phosphate only	5.35	0.550	2.38	3

crystalluria was certainly higher in stone formers than in normal subjects, it is not surprising that as shown in Figures 2 and 3 the differences between the normal subjects and the untreated stone formers were not clear cut.

Two questions are posed by these results. Firstly, does the presence of crystals in evaporated normal urine samples indicate those normal subjects who would make stones under conditions of chronic dehydration? Secondly, does the absence of crystals in the stone formers indicate that they are no longer metabolically active? If these questions could be answered affirmatively it would in fact be postulated that the evaporation test really does distinguish quite clearly the stone formers from the normal subjects and that the reasons for this not being obvious is that individuals have been allocated to the wrong groups. Such a postulate is clearly not proven; much more evidence will be required before it can be substantiated or refuted and it is put forward only as a working hypothesis for further testing. Nevertheless, regardless of whether or not the postulate is accepted, the evaporation technique can still be used as a clinical test. Thus if 2 samples from a single untreated stone former were tested, the probability of not finding crystals in either sample would fall to 1.8%. It is therefore suggested that a test for active stone formation might be based upon evaporation of 2 urine samples. If neither of these showed crystals then the subject would not be at risk of stone formation. However, under these conditions 72% of normal subjects would also show crystals, so that the positive findings would not be a distinguishing feature in this test.

The response to this test of urine samples from stone formers undergoing treatment with thiazide diuretics and/or cellulose phosphate is of interest.

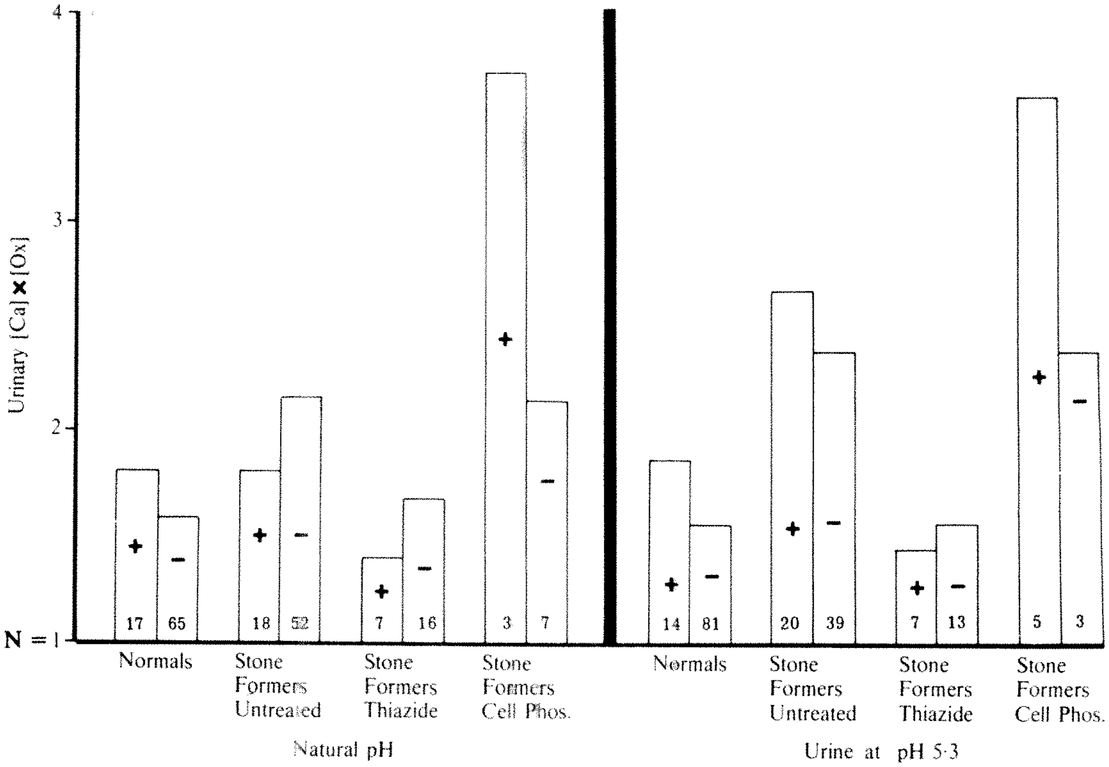


Fig. 4 The calcium X oxalate concentration products in evaporated urine samples from normal subjects and the stone formers with (+) and without (−) oxalate crystalluria.

It is seen in Figure 2 that thiazide increases the incidence of samples without crystals by a factor of 2, whereas cellulose phosphate increases the incidence of crystal in urine to 100%, a most surprising result with a therapy which is intended to reduce stone formation. However, it is to be noted that the increase in crystal formation with cellulose phosphate is mainly in the post-evaporation samples and patients are, of course, advised to drink water rather than to restrict it. The test seems to indicate that it might be particularly dangerous for patients on cellulose phosphate therapy to allow their urine to become concentrated, say by exposure to a hot environment and failure to drink sufficient water. The explanation of these findings is presumably that although cellulose phosphate lowers urinary calcium (Dent *et al.*, 1964), it also lowers urinary magnesium (Dent *et al.*, 1964; Teotia *et al.*, 1974) and raises urinary oxalate (Marshall and Barry, 1973; Hallson *et al.*, 1977) and phosphate (Dent *et al.*, 1964). Combined treatment with thiazide and cellulose phosphate resulted in an increase of crystal-free urine samples to the normal value and this treatment would therefore seem to be advantageous.

The results of testing the urine samples at pH 5.3 are shown in Figure 3. Under these conditions phosphate crystals are greatly reduced and oxalate crystals increased, so that such a test might be considered helpful if one believes that oxalate is more important than phosphate with regard to the common "metabolic calcium oxalate/phosphate" stones. At pH 5.3 crystal formation is again least common in the normal subjects but still occurs in 20%, is more common in untreated stone formers (53.5%), rises slightly with treatment with thiazide and more with cellulose phosphate (70%). Again the combination of thiazide and cellulose phosphate is the most effective therapy in reducing urinary crystals, and with this treatment the incidence was zero before evaporation and 20% after evaporation.

The formation of crystals of a chemical in urine is only possible if the solubility (product) of the chemical is exceeded. Even then crystalluria may be prevented by inhibitors of crystal formation and

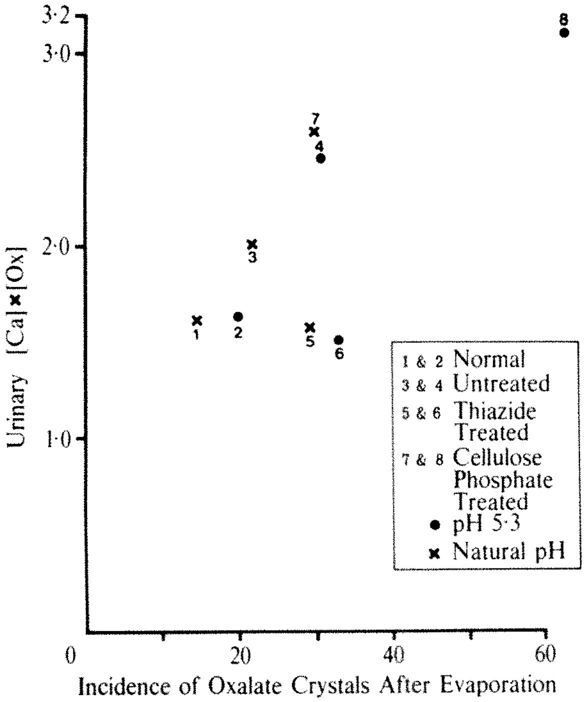
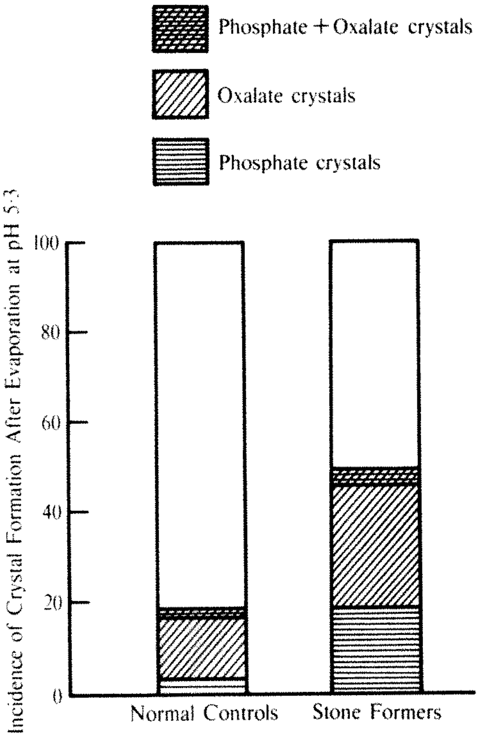


Fig. 5 Mean post-evaporation urinary calcium and oxalate concentration product plotted against incidence of oxalate crystals in the same samples in various conditions. X = natural pH; ● = pH 5.3; 1 and 2 are normal subjects and the rest are stone formers; 3 and 4 untreated; 5 and 6 treated with thiazide; 7 and 8 treated with cellulose phosphate.



	Normal Controls	Stone Formers
N =	95	33
[Ca] [Ox] =	1·61	1·55
Phosphate m mol/L =	26·17	15·68
pH =	5·3	5·3

Fig. 6 Incidence of phosphate and oxalate crystals among normal controls and stone formers with matched means and distribution of calcium and oxalate concentration products (see text).

of crystal growth. In this study measurements were made of urinary concentration of calcium, phosphate and oxalate and it is of some interest to see whether or not crystalluria was linked with mineral composition or whether the role of inhibitors was more important. In Figure 4 the products of calcium and oxalate concentration, henceforward referred to as [Ca Ox], are compared in urine samples with and without crystals respectively. It can be seen that the product is higher in stone formers than in normal subjects and lowered by thiazide and raised by cellulose phosphate, and it has been shown that all these differences are statistically significant. These results suggest that, as one might suppose, the concentration of calcium and oxalate are important factors in stone formation. However, there is a lack of correlation between the incidence of crystal formation and [Ca Ox] and this can be shown in several ways. Firstly, although Figure 4 shows that in normal subjects crystal formation was associated with a higher product than was absence of crystal, the reverse was true for untreated stone formers at normal pH and for stone formers treated with thiazide and with urine of pH 5.3. However, these differences are not statistically significant and when the products for urine with and without crystals in each group of Figure 4 are compared, there are no statistically significant differences. Secondly, in Figure 5, where incidence of oxalate crystals in various groups is plotted against [Ca Ox], the correlation is remarkably poor. Thirdly, Figure 6 shows that the differences in incidences of crystals at pH 5.3 between normal subjects and stone formers does not depend upon the differences in [Ca Ox]. It is therefore concluded that although [Ca Ox] is raised in stone formers and altered by treatment, the differences in incidence of crystal formation are not explained solely by those changes, with the possible exception that the very large changes in urinary chemical composition induced by cellulose phosphate may be an important cause of the increased crystal incidence associated with this drug. In all other cases the changes in urine mineral composition do not account for changes in crystalluria and it is therefore necessary to postulate that the inhibitors of crystal formation play an important role in determining whether or not a urine will show crystal formation.

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Risk Factors in Calcium Stone Disease of the Urinary Tract

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Summary—The concept that calcium stone formation may be explained on the basis of a number of risk factors is developed. The main risk factors involved are shown to be calcium, oxalate, pH, acid mucopolysaccharides and uric acid.

A method is described for calculating and combining the individual risk factors into a measure of the "relative probability" of forming stones (P_{SF}).

P_{SF} values are generally lower in normal subjects than in stone-formers. Amongst the normals, P_{SF} values are lower in children and women than in men.

Recurrent stone-formers have the highest P_{SF} values and these correlate well with the severity of the disease as defined by the stone episode rate of the patient. Single stone-formers have P_{SF} values intermediate between those of normal men and those of recurrent stone-formers.

It has been apparent for many years that calcium stone disease is a multifactorial disorder. In recent years, however, it has been shown that there are 2 main chemical factors which seem to determine the risk of forming calcium-containing stones, namely, the degree of saturation of urine with calcium oxalate and calcium phosphate and the level of protective inhibitory activity against the crystallisation of calcium oxalate (Robertson *et al.*, 1969, 1971; Robertson and Peacock, 1972; Robertson *et al.*, 1976; Smith, 1976). Since urinary calcium, oxalate and pH are the major determinants of urine saturation with calcium salts (Robertson and Nordin, 1976), it is likely that the risk of forming stones is related to the level of these constituents in urine. In addition, the risk of forming stones is related to the concentration of urinary inhibitory activity, the majority of which appears to be in the acid mucopolysaccharide (AMPS) fraction of urine (Robertson *et al.*, 1973, 1976). Recently it has been shown that a high excretion of uric acid may interfere with this inhibitor (Robertson *et al.*, 1976). Thus there appear to be 5 main constituents of urine (*i.e.* calcium, oxalate, pH, AMPS and uric acid) which influence the risk of large crystals of calcium oxalate forming in urine, crystals which may aggregate sufficiently to be trapped in the urinary tract.

The objects of this paper are to develop the concept that calcium stone formation may be explained on the basis of a number of "risk factors" and, then, from these "risk factors" to derive a measure of the overall probability of forming stones.

Patients and Methods

In the first part of the study, 24-h urine samples were collected with preservative from a total of 120 male, recurrent, idiopathic stone-formers who had formed calcium oxalate-containing stones. For some of the studies, the patients were divided into 2 groups according to their stone analysis. The first group, whose stones consisted almost entirely of calcium oxalate, were defined as "pure" calcium oxalate stone-formers. The second group, whose stones contained calcium oxalate and calcium phosphate, were termed "mixed" calcium oxalate/calcium phosphate stone-formers. Twenty-four-hour urines were also collected from a total of 100 male normal controls. The entire study was carried out on a "free diet".

In the second part of the study, 24-h urines were collected from 38 normal subjects (6 children, 22 women and 10 men), from 22 untreated calcium stone-formers who had formed only one stone during their lives, and from 50 untreated recurrent stone-formers who were attending a urological out-patient clinic.

Read at the 34th Annual Meeting of the British Association of Urological Surgeons in Brighton, June 1978.

The urines in the first part of the study were analysed for pH, calcium, magnesium, sodium, potassium, ammonium, phosphate, oxalate, citrate, sulphate, uric acid and acid mucopolysaccharides (AMPS) by methods previously described (Robertson *et al.*, 1968; Whiteman, 1973). The urines in the second part of the study were analysed for only pH, calcium, oxalate, AMPS and uric acid.

In the first part of the study, the mean values ±1SEM for each constituent were calculated and compared in the recurrent stone-formers and normals. The frequency distributions of the 5 variables whose mean values were found to be significantly different in the 2 groups were used to calculate the "risk" of being a stone-former at each value of all the 5 variables concerned. A set of "risk curves" for the 5 variables was produced and used to calculate the overall "relative probability" of being a stone-former.

Results

The results of the 24-h urine analysis in recurrent stone-formers and normals are given in the Table. This shows that of the 12 variables measured, the only ones to be significantly different in stone-formers and normals were calcium ($P < 0.001$), oxalate ($P < 0.001$), AMPS ($P < 0.02$) and uric acid ($P < 0.05$). In addition, the urinary pH of "mixed" calcium oxalate/calcium phosphate stone-formers was higher than in both "pure" calcium oxalate stone-formers and normal subjects ($P < 0.01$). The smoothed frequency distributions of the 24-h excretion of these 5 urinary constituents in stone-formers (SF) and normals (N) are shown in Figures 1 and 2. Although the mean values for each of these factors are significantly different between stone-formers and normals, there is a large degree of overlap between the values in the 2 populations. However, Figure 1 shows that the higher the urinary excretion of calcium and oxalate and the higher the urinary pH, the greater the risk of being a stone-former. Similarly, Figure 2 shows that the lower the excretion of AMPS and the higher the excretion of uric acid, the greater the risk of forming stones.

Figure 3 shows a possible way of quantitating this increase in the risk of stones as urinary calcium increases. The top part of the diagram shows again the frequency distributions of urinary calcium in the recurrent stone-formers and normals taken from Figure 1. The lower half of the diagram shows the ratio (α) of the (frequency of stone-formers)/(frequency of normals) at each level of calcium excretion. Clearly, the "odds" of being a stone-former increase as urinary calcium increases, the curve rising sharply above an excretion of 10 mmol/day. This ratio (α) has been termed the "relative risk factor" for, in this instance, calcium, and the curve of αCa against urinary calcium, the "risk curve" for calcium.

Table The mean values ± 1SEM of the 24-h Excretion of Various Urinary Constituents in Recurrent Stone-formers and Normal Subjects

Variable		*Normals*	*Recurrent Stone-formers*		*P*
	n	*Mean SEM*	*n*	*Mean SEM*	
pH	60	5.92 ± 0.06	*14	6.23 ± 0.06	<0.01
			†16	5.88 ± 0.05	ns
Ca (mmol)	60	5.95 ± 0.35	65	8.00 ± 0.38	<0.001
Mg (mmol)	60	4.48 ± 0.21	30	5.05 ± 0.25	ns
Na (mmol)	60	172 ± 8	30	194 ± 10	ns
K (mmol)	60	59 ± 3	30	62 ± 3	ns
NH_4 (mmol)	60	39 ± 5	30	34 ± 4	ns
PO_4 (mmol)	60	28.8 ± 1.1	30	29.7 ± 1.8	ns
Ox (mmol)	60	0.35 ± 0.01	65	0.43 ± 0.02	<0.001
Citrate (mmol)	60	3.22 ± 0.18	30	3.19 ± 0.20	ns
SO_4 (mmol)	60	22.5 ± 1.0	30	25.0 ± 1.6	ns
AMPS (mgmol)	20	20.2 ± 1.4	25	14.7 ± 1.3	<0.02
Uric acid (mmol)	20	2.9 ± 0.2	65	3.4 ± 0.1	<0.05

* For stone-formers producing "mixed" calcium oxalate/calcium phosphate stones.
† For stone-formers producing "pure" calcium oxalate stones.

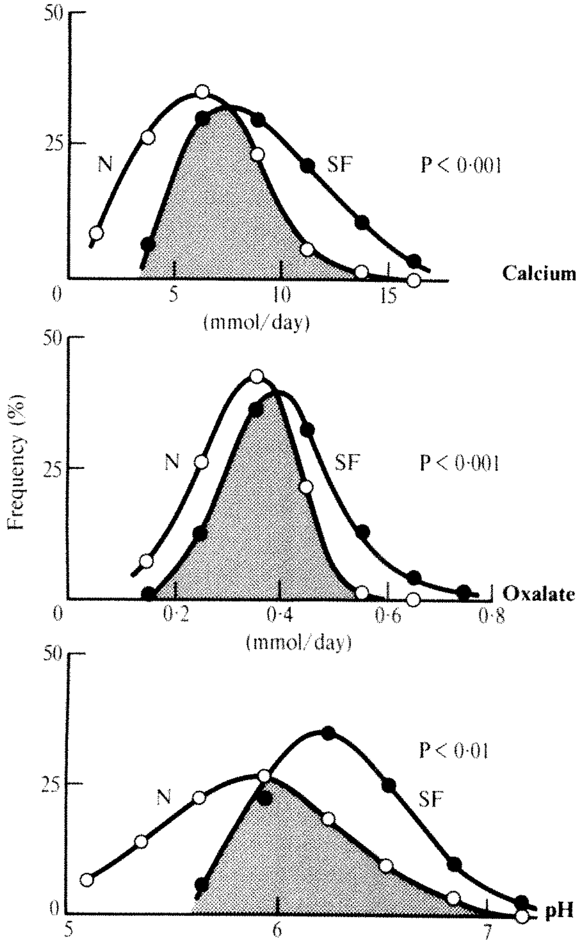

Fig. 1 Frequency distributions of 24-h urinary calcium and oxalate excretions and urinary pH in normal subjects (o) and recurrent stone-formers (•). The shaded area defines the region of overlap between the 2 populations.

This type of analysis may be applied to the frequency distributions of urinary oxalate, pH, AMPS and uric acid to obtain risk curves for each of these factors. These, together with the risk curve for calcium, are shown in Figure 4, in which the relative risk (α) attributable to each constituent is plotted in relation to the number of standard deviations (SD) above and below the mean value for each constituent in the normal population. On this basis, it is then possible to compare the relative importance of each constituent as a risk factor in the formation of calcium-containing stones. Figure 4 shows that, *per se*, urinary oxalate is the most

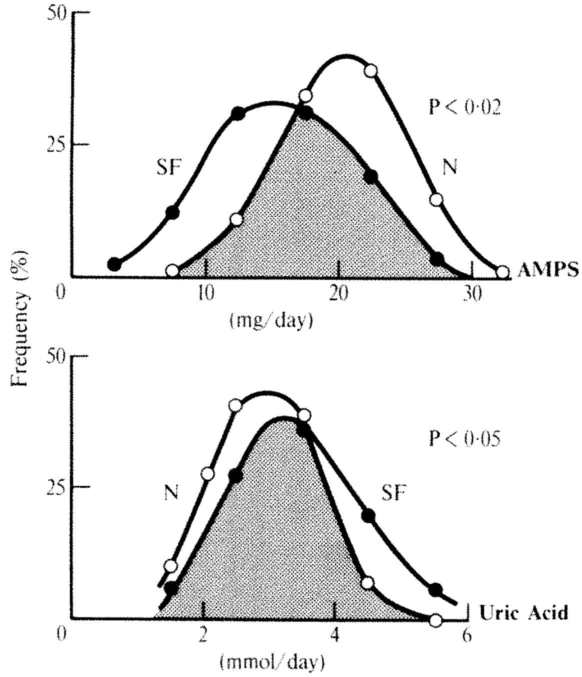

Fig. 2 Frequency distributions of 24-h urinary excretion of acid mucopolysaccharides (AMPS) and uric acid in normal subjects (o) and recurrent stone-formers (•). The shaded area defines the region of overlap between the 2 populations.

critical factor, whereas increases in calcium and pH are less important in causing stones to form.

The relative risk factors (α_{Ca},α_{Ox},α_{pH},α_{AMPS} and α_{UA}) may be combined into an overall relative probability of being a stone-former (Psf) by using the equation:

$$P_{SF} = \frac{\alpha_{Ca}\alpha_{Ox}\alpha_{pH}\alpha_{AMPS}\alpha_{UA}}{(1 + \alpha_{Ca}\alpha_{Ox}\alpha_{pH}\alpha_{AMPS}\alpha_{UA})}$$

the value of Psf lying between 0 and 1.

By measuring urinary pH and the excretions of calcium, oxalate, AMPS and uric acid in a 24-h urine sample from a given individual it is possible to derive a measure of his risk of forming calcium-containing stones.

Figure 5 shows the relative probability of forming stones in groups of normal children and adults and in groups of single and recurrent calcium stone-formers. This demonstrates that normal subjects have values of Psf between 0.001 and 0.34 and that Psf his lowest in children but rises through normal women and is highest among normal men.

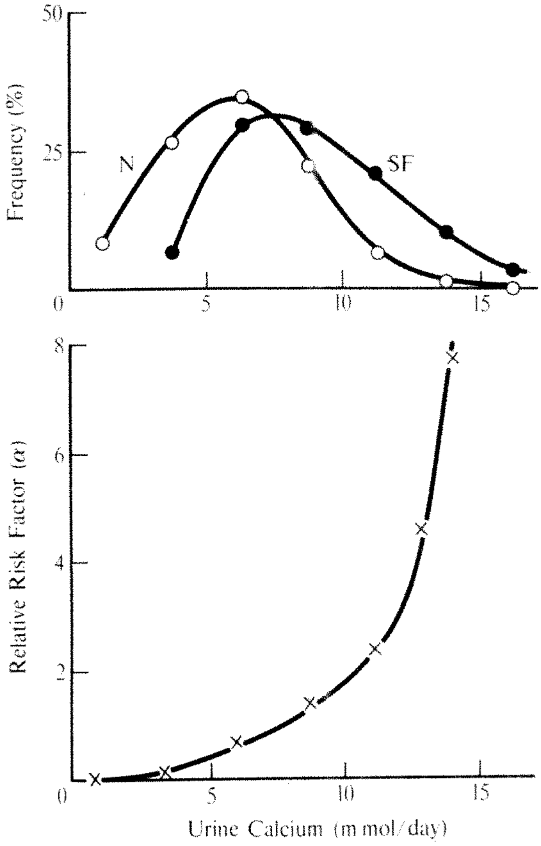

Fig. 3 Top: Frequency distributions of 24-h urinary calcium in normals (N) and recurrent stone-formers (SF). Bottom: The ratio (α) is the frequency of stone-formers/frequency of normals at various levels of calcium excretion.

Recurrent stone-formers have values of PSF between 0.28 and 0.99 and have very little overlap with normal men. Single stone-formers have values overlapping with those of normal men and recurrent stone-formers.

Figure 6 shows that among the recurrent stone-formers, the severity of the disease (as defined by the stone episode rate of each patient) is proportional to his calculated relative probability (PSF) of forming stones. Above PSF values of 0.6 the relationship rises steeply and approaches a value of 1 asymptotically, as would be expected since probability can never exceed a value of 1.

Discussion

It has been known for many years that cystine stone formation occurs only in subjects who have an excessive urinary excretion of cystine resulting from a genetic defect in the tubular reabsorption of cystine. The frequency distributions of cystine excretion in normal subjects and in homozygous cystinuric stone-formers do not overlap at all (Crawhall *et al.*, 1969). The reason why non-cystinuric subjects do not form cystine stones is that cystine excretion must exceed about 1250 μmol/day before precipitation will take place in urine (Dent and Senior, 1955). Normal subjects generally excrete much lower levels of cystine, whereas most homozygous cystinurics excrete levels well in excess of the solubility value.

In calcium oxalate stone formation, however, there is no such clear-cut separation between matched populations of stone-formers and normals for any of the factors involved (Figs. 1 and 2). It follows that calcium stone formation is unlikely to have a single cause, as does cystine stone formation, but must be considered to arise from a combination of risk factors, as in ischaemic heart disease.

This paper describes an attempt to combine 5 of the main risk factors known to be involved in the genesis of calcium-containing stones. Of these factors, calcium, oxalate and pH together control the saturation of urine with calcium salts (Robertson and Nordin, 1976) and AMPS and uric acid largely determine the inhibitory activity of urine (Robertson *et al.*, 1976). When one or more of these factors is increased (or decreased as in the case of AMPS) the calculated relative probability of forming stones (PSF) rises and there is a greater risk of a stone being formed.

In practice, PSF discriminates well between recurrent stone-formers and normals and accounts for the very low incidence of idiopathic stones among children and the relatively low incidence among women. PSF also correlates well with the severity of the disease in recurrent stone-formers. The fact that single stone-formers have such a wide range of PSF values is interesting. Presumably some of these patients will eventually become recurrent stone-formers and some will not form any further stones. It will be interesting to see whether or not the patients with the high PSF values join the recurrent stone-formers and whether or not the patients with the low values form no more stones.

In conclusion, it is hoped that this technique of combining risk factors will provide, firstly, a useful means of assessing a patient who presents with stones. Secondly, it may also be used as a screening procedure for identifying individuals in the general population who are at risk of forming stones.

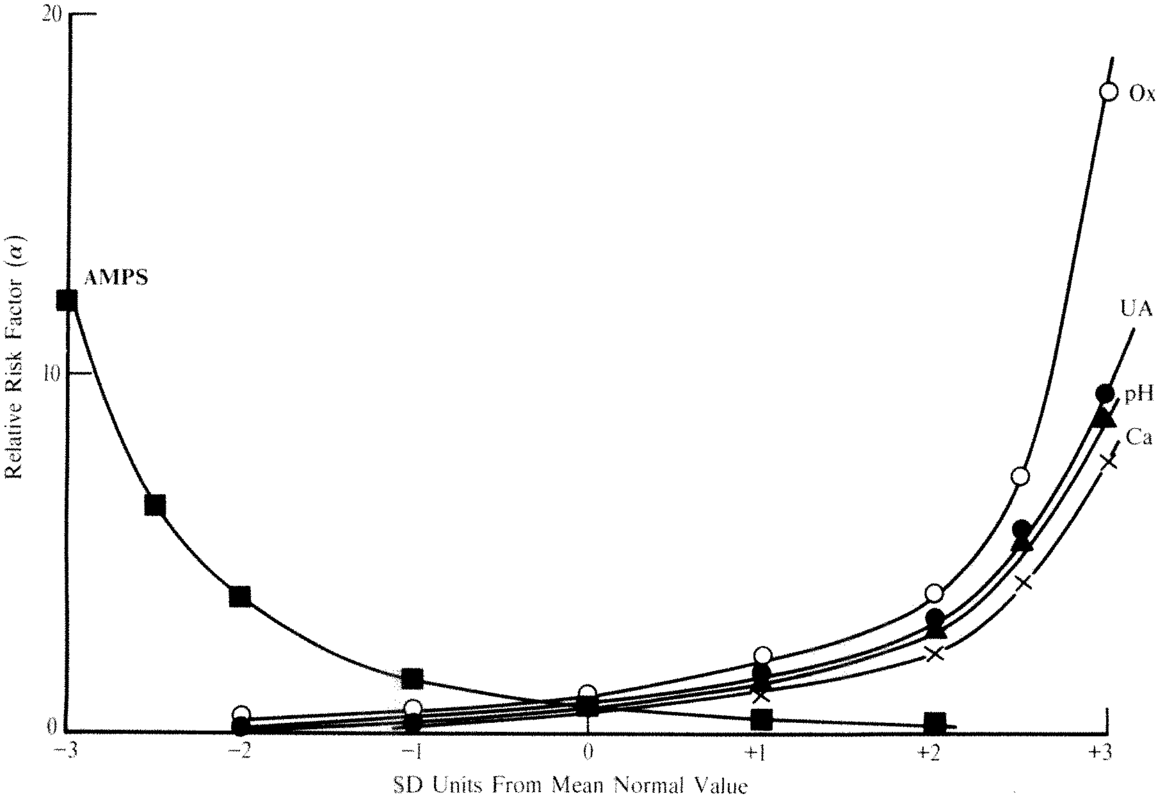

Fig. 4 The "risk curves" for calcium, oxalate, pH, AMPS and uric acid plotted in relation to the number of SD units around the mean value in the normal population.

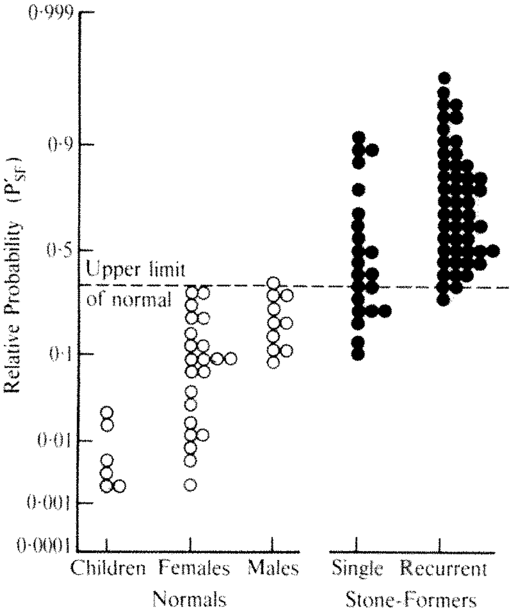

Fig. 5 The overall relative probability of forming stones in normal children and adults and in single and recurrent stone-formers.

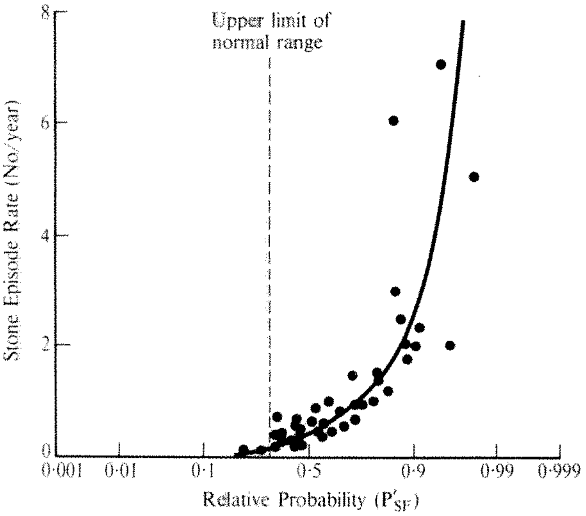

Fig. 6 The stone-episode rate in recurrent calcium stone-formers in relation to their calculated overall relative probability of forming stones.

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Finally, it may enable the clinician to formulate a rational course of treatment for the patient and allow him to assess the progress of the patient during the treatment period.

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The Effect of Allopurinol on Urinary Oxalate Excretion in Stone Formers

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Summary—Allopurinol is a drug which could be valuable in the treatment of stone patients. In 29 subjects treated with 300 mg of the drug per day it has been found that there was a significant fall in urine oxalate excretion if the blood urate was above 330 μmol/l. In 10 subjects followed for 1 year the urine oxalate was significantly reduced and maintained at a lower level than the original.

Urologists are very aware that once a patient has a stone episode then it is likely to recur (Sutherland, 1954; Williams, 1963). In order to minimise the likelihood of recurrence it is essential that every effort should be made to eradicate infection and to eliminate possible underlying metabolic abnormalities such as hyperparathyroidism.

In certain centres it has become common practice to reduce urinary constituents associated with stone formation by drug therapy. One such drug which has caused some interest is allopurinol and it has been stated that it merits further careful study in its role of stone prevention (Yendt and Cohanim, 1976).

Patients and Methods

The aim of the present study was to measure the effect of allopurinol on urinary oxalate output. Forty subjects (30 male, 10 female) were given 300 mg of the drug daily for one year. This dose of drug was given in one tablet and was taken after breakfast. Twenty-four-hour urine samples were collected before commencement of treatment and were analysed for their oxalate (Hodgkinson and Williams, 1972), phosphate, urate, calcium and zinc contents. Serum was analysed for calcium, phosphate, urate, urea and electrolytes. All the urine oxalate measurements were undertaken by one person (A.M.), the other measurements being undertaken in the routine biochemical laboratory. At 3-monthly intervals all measurements were repeated and care was taken to ensure that the patients were not on any therapy known to increase blood urate values.

In 29 subjects paired results are available and in 10 subjects therapy and measurements are complete at one year.

Results

In the first preliminary study paired oxalate estimations were analysed in 13 subjects. It was found

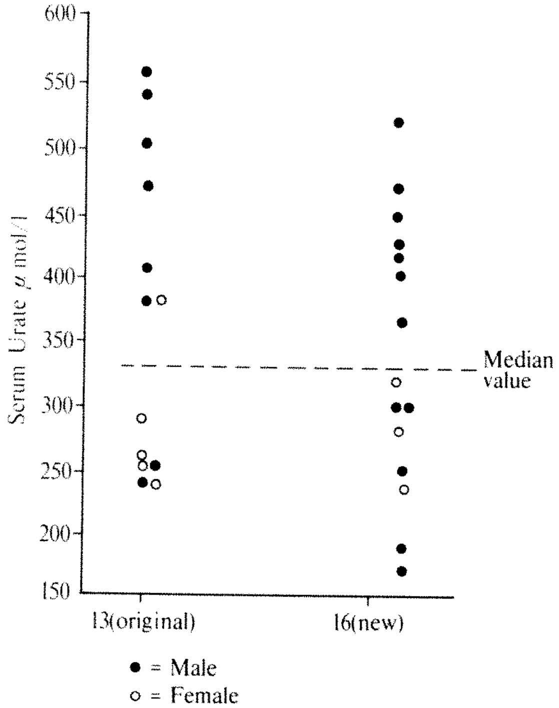

Fig. 1 Initial serum urate values (μmol/l) in original 13 and 16 new subjects. Median value 330 μmol/l.

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that there was a significant fall ($P>0.05$) in urinary oxalate output after 3 months (Scott *et al.*, 1978).

Encouraged by this finding, the next 37 patients were dealt with in a similar manner. In a further 16 subjects paired oxalate measurements were available. Analyses of the results in these 16 patients did not show a significant fall in urine oxalate values. However, when the initial blood urate values were studied and graded it was found that in the 29 subjects the mean value was 330 µmol/l (Fig. 1). When the 29 subjects were divided at this median value of serum urate, then it was found that in those who had blood urate values in excess of the median value there was a significant fall in urine oxalate ($P>0.05$) excretion after 3 months' therapy (Table). In the remainder of the subjects the fall in oxalate excretion was not significant (Fig. 2).

Table Urine Oxalate Excretion (mg/24 h) Before and After Allopurinol in 29 Subjects*

Group I		*Group II*	
Initial	*3 months*	*Initial*	*3 months*
38.9	19.4	45.9	26.0
46.2	38.5	35.1	47.9
48.9	33.8	62.0	57.1
40.8	26.4	31.9	66.9
95.8	37.5	41.6	42.7
37.8	30.3	30.8	37.6
33.6	48.2	45.5	43.5
36.4	45.6	56.3	50.9
26.0	6.0	50.9	47.7
18.8	13.9	28.9	12.0
45.9	27.4	30.2	17.6
63.0	36.3	27.6	24.6
60.2	41.7	33.1	34.6
88.3	45.9	22.9	36.4
31.8	60.2		

*Group I : Initial plasma urate >330 µmol/l
Group II: Initial plasma urate <330 µmol/l

In 10 subjects who have been on therapy for one year there is a significant fall in urine oxalate excretion which has been maintained (Fig. 3) (median 48.5 falling to 37.6 mg oxalate/24 h).

There has been no significant change in outputs of calcium, magnesium, zinc, urate or phosphate. Two subjects have had to be withdrawn from the trial after 5 and 6 months respectively because of possible drug-induced side effects, namely skin rashes, joint pain and gastrointestinal symptoms.

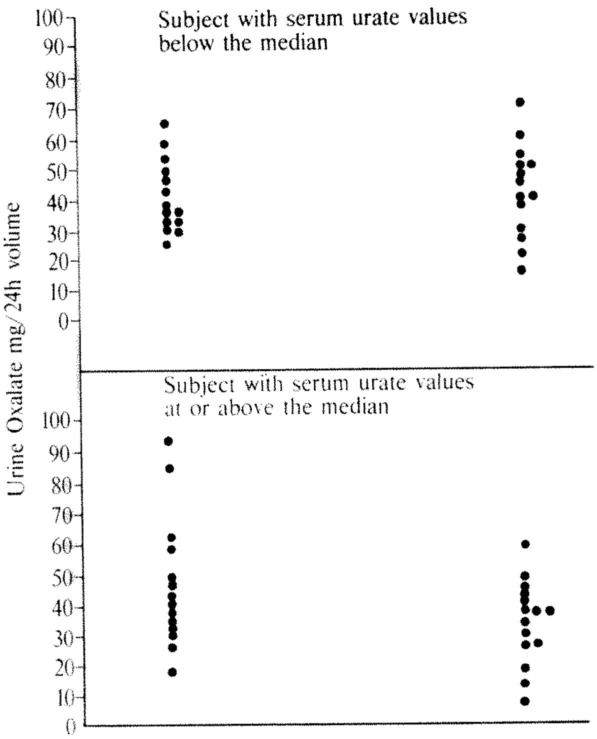

Fig. 2 Changes in urine oxalate in subjects with serum urate above median (significant) and below median serum urate (not significant).

Discussion

Recurrence of stone disease is a very complex subject. With the awareness of the likelihood of recurrence a conservative surgical approach is advocated (Williams, 1972). When dealing with a metabolic stone or where there is an accompanying renal abnormality such as renal tubular acidosis (Williams and Chisholm, 1976) it can be expected that the recurrence rate will be higher than when dealing with a phosphatic type of stone, provided that infection can be eliminated (Sleight and Wickham, 1977). What is certain is that with the passage of time a recurrence of stones becomes more likely and may even reach as high as 34% 20 years after the initial stone presentation (Rose and Follows, 1977).

Faced with the growing evidence that stone disease is of a recurrent nature, a variety of substances has been used in an effort to reduce the excretion of stone-forming substances in urine. Most workers have concentrated on reducing urinary excretion of calcium, using such substances as cellulose phosphate (Dent *et al.*, 1964; Pak, 1973) or a thiazide diuretic (Yendt *et al.*, 1966; Yendt, 1970).

The first indication of a possible connection

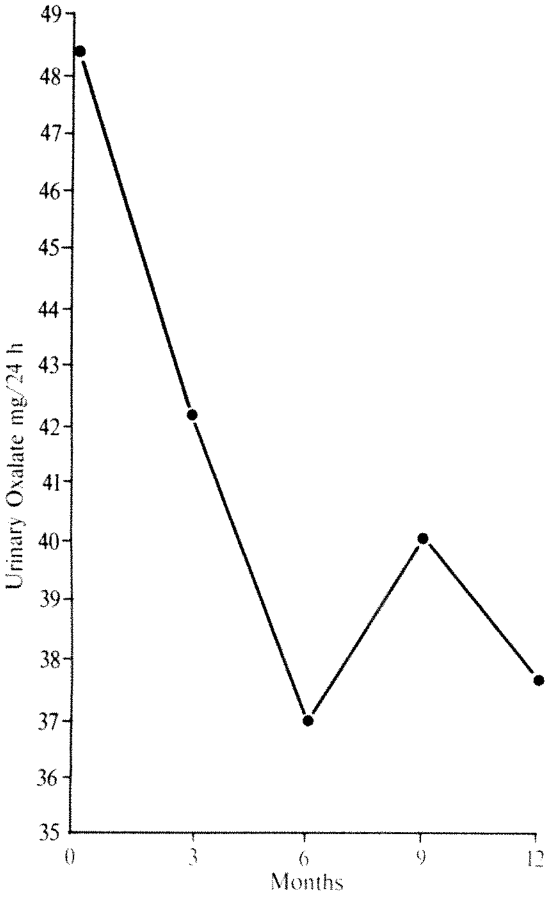

Fig. 3 Effect of allopurinol on urinary oxalate levels in 10 subjects followed for 1 year (median values).

between uric acid metabolism and urinary oxalate excretion came when it was observed that uric acid interfered with urinary oxalate solubility (Mayer *et al.*, 1968) and this has been confirmed (Smith *et al.*, 1969; Robertson *et al.*, 1971). Searching for possible connections between uric acid and oxalate metabolism, Smith and Boyce (1969) speculated that the link may be the enzyme xanthine oxidase. Following Smith's observation it was noted that in 21 stone formers who had hyperuricaemia and/or hyperuricosuria, treatment with allopurinol caused a dramatic fall in the occurrence of further stone problems (Coe and Raisen, 1973). This finding has been confirmed by other studies (Smith *et al.*, 1969; Smith, 1977).

There is therefore a growing awareness that uric acid may be very important in influencing urinary oxalate excretion. Further evidence of the importance of urate metabolism in stone formation is the observation that monosodium urate is the stable form of urate in urine at pH 6 and this type of urate may form a nucleus for stone formation (Pak *et al.*, 1977). Urologists also need to be aware that tubular function is impared in patients with asymptomatic hyperuricaemia (Nishida *et al.*, 1977).

The present study gives support to the importance of blood uric acid levels on urine oxalate excretion. Even if the subject does not have a blood urate above the normal range but is 'high normal' it is possible to reduce urine oxalate significantly with a drug known to be singularly free from side effects.

Acknowledgement

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The Influence of Refined Carbohydrate on Urinary Calcium Excretion

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Summary—In the course of study of the influence of varying the amount of refined carbohydrate (sugar and sugar products) in an otherwise standardised diet in 18 normal subjects it was evident that the analysis of 24-h urine collections failed to show the profound diurnal variation in urinary electrolyte excretion and, in particular in this instance, calcium excretion.

The analysis of individually voided specimens showed some normal subjects to have spontaneously high peaks of urinary calcium concentration throughout the day even whilst on a diet with low refined carbohydrate content. Increase in the refined carbohydrate content of the otherwise standardised diet caused significant increase in the number of urines with a calcium concentration above 9 mmol/l.

Refined carbohydrate, a common constituent in Western diets, can therefore influence urinary electrolyte excretion in such a way that there may be an increased risk of over-saturation with calcium oxalate.

The epidemiology of calcium stone of renal origin suggests that the structure of the diet is an important factor in a multifactorial aetiology (Blacklock, 1976, 1977). The condition has become more common as communities have become affluent (Inada *et al.*, 1958; Andersen, 1969), whilst it remains rare in those still living in poor or primitive conditions (Modlin, 1967). The most constant accompaniment of transition from poverty to affluence is a change in eating habit which is characterised by increase in consumption of fat, animal protein and refined carbohydrate, the increase in the latter being substantial (Cleave, 1974; Blacklock, 1976). Concurrently there is depletion of crude dietary fibre (Burkitt and Trowell, 1975) with its satiating properties, the result of which is to encourage over-consumption and therefore over-nutrition (Haber *et al.*, 1977).

Any connection between an altered dietary structure and increased incidence of idiopathic calcium stone, in which calcium oxalate predominates, must lie in changes which this dietary structure can bring about in the profile of urinary constituents. Such changes should increase the risk of calcium oxalate crystallisation.

Both protein and available carbohydrate are known to alter urinary electrolyte excretion, particularly the rate of calcium excretion (Hodgkinson and Heaton, 1965; Lindeman *et al.*, 1967). Sugar ingested in bolus form has been shown to cause acute changes in urinary calcium and magnesium excretion which are more marked in idiopathic stone formers (Lennon, *et al.*, 1968). Between 30 and 50% of idiopathic renal stone formers have hypercalciuria (Blacklock and Macleod, 1974) but almost all of these have normal rates of urinary calcim excretion whilst fasting, indicating the role of nutrients in inducing calciuria either directly or indirectly (Peacock and Nordin, 1969).

Although protein can also induce changes in calcium excretion (Hodgkinson and Heaton, 1965), we have chosen to examine the influence of different amounts of refined carbohydrate in the diet since this nutrient is more rapidly assimilable and therefore more likely to have a demonstrable effect on renal excretion. We are also investigating whether crude fibre supplementation of the diet can modify nutrient-induced effects of renal excretion.

This paper describes the effect of variation in the amount of refined carbohydrate on the excretion of calcium, the diet being standardised for all other nutrients and containing no crude fibre supplements.

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Patients and Methods

It has been our experience in controlled environmental chamber studies that the content of electrolytes such as calcium in a 24-h collection gives little indication of rates of excretion and no indication of the time and magnitude of peaks of concentration throughout the day. Similar observations have been made in respect of oxalate (Hargreave *et al.*, 1977). In view of this we considered that if various amounts of dietary nutrient affected the urinary excretion of electrolytes, this would be more readily demonstrable by the analysis of individual urine specimens.

Nineteen healthy young white male subjects were observed in a large self-contained metabolic chamber for a month. The subjects were fully informed volunteers. Initial medical examination included personal and family history, chest X-ray, ECG, exercise tolerance test and oral glucose tolerance test. None of the subjects had received thiazides, anticonvulsants, steroids, supplemental phosphates or vitamin D, and none was on current drug therapy. One subject was withdrawn during the course of the experiment because his glucose tolerance test was pre-diabetic by the criteria of Jarret *et al.* (1977). Mean age of those who completed the experiment was 20.2 years (range 17 to 24); mean weight was 73.6 kg (range 57.8 to 90.5 kg) and mean relative weight was 1.02 compared to average for age and height (Society of Actuaries, 1959).

The experimental design was that of 2 separate cross-over trials. In the first trial (11 subjects) urinary excretion of calcium while on a "low" carbohydrate diet (LCD) (200 g available carbohydrate of which 110 g was sucrose) was compared with that observed in the same subjects while on a "normal" carbohydrate diet (NCD) (400 g available carbohydrate of which 220 g was sucrose). At the beginning of the period subjects were randomly allocated to either the LCD or the NCD; on Day 15 the diets were crossed over. Design of the second trial (7 subjects) was identical except that the 2 experimental diets were the LCD and a "high" carbohydrate diet (HCD) (600 g available carbohydrate of which 330 g was sucrose). The experimental diets varied only in their content of available carbohydrate. Standardised daily intake of other nutrients was as follows: protein, 115 g; fat, 170 g; calcium, 35 mmol; phosphorus, 60 mmol; no distinction was made between animal protein and that of vegetable origin. Subjects were maintained in a steady state of physical fitness during their stay in the metabolic chamber by means of individually-prescribed regimens of exercise.

Urine was collected as voided, although subjects were encouraged to micturate at the set times of 0600, 0900, 1130, 1430, 1730 and 2300. Aliquots were taken from each specimen passed and stored at −20°C until analysis. Urinary content of calcium was determined using a carrier of aqueous solution of lanthanum (Willis, 1961; Trudeau and Freier, 1967) in the Pye Unicam SP 191 single beam atomic absorption spectrophotometer linked to an autosampler and external digital printer. Blank solutions and control standards were interspersed among the subject samples. Quality control standards in use require repeatability of better than 1% (coefficient of variation) utilising pooled urines. Recovery rates of calcium added to urine ranged between 89 and 103%, with a mean of 97%.

Results

The results of analyses of pooled 24-h collections of urine showed no significant difference in excretion rates of calcium when the available carbohydrate content of the diet was increased from 200 (LCD) to 400 g per day (NCD). There was a slight but not significant increase in calcium excretion in subjects whose dietary content of available carbohydrate was increased from 200 (LCD) to 600 g per person per day (HCD) (Table). Since the 24-h urine collection includes urine excreted during the fasting overnight period when, even in known hypercalciurics, the rate of calcium excretion tends to return to normal, these results confirmed that the use of 24-h collections was inadequate in attempting to evaluate the effect of diet on the excretion rates of urinary electrolytes, and that the analysis of individually voided specimens passed at the specified times throughout the day was necessary.

When 19 normal subjects were taking the LCD, the 880 urine specimens voided during the second week on this regime had a mean calcium concentration of 3.8 mmol/l and the upper 95% confidence limit was 8.2 mmol/l (Fig. 1). When 9 mmol/l were arbitrarily chosen as the upper limit of calcium concentration, *i.e.* more than 2 standard deviations above the mean, only 29 specimens (3.3%) were found to exceed this.

When 18 of the original 19 subjects took either

Table The 24-h urinary calcium excretion in millimoles per man per day with ean, grand mean and standard deviation (SD) in normal subjects taking a standard diet containing 200 g of carbohydrate (L 400 g (NCD) and 600 g (HCD) per day.

	During Second Week of a Diet Reduced to 200 g COH man^{-1} day^{-1}								*During 6 Days on a Normal* (400 g man^{-1} day^{-1}) COH Intake							
	Days						*Mean*	*Grand Mean and S.D.*	*Days*						*Mean*	*Grand Mean and S.D.*
101	5.0	5.9	6.0	4.3	3.4	6.5	5.2		4.6	4.9	5.7	9.1	5.3	7.6	6.2	
102	5.7	5.4	6.6	4.6	7.0	6.7	6.0		3.5	5.5	5.1	6.3	7.3	6.9	5.8	
103	5.8	7.2	3.2	4.8	5.0	6.5	5.4		5.7	7.0	7.1	6.5	3.5	7.1	6.2	
104	9.6	9.2	11.4	10.4	10.8	8.5	10.0		8.5	8.5	11.2	10.5	5.4	8.5	8.8	
105	10.1	11.7	11.8	9.4	10.7	11.1	10.8		8.6	14.4	15.3	16.4	12.0	14.4	13.5	
106	10.8	14.0	10.0	11.4	10.2	10.2	11.1		8.8	13.4	11.1	8.0	8.2	11.2	10.1	
107	10.9	8.3	7.6	8.6	12.9	8.4	9.5		12.3	9.8	11.1	12.1	11.4	11.8	11.4	
108	7.5	6.5	6.8	6.4	5.7	8.5	6.9		8.1	8.3	10.6	9.6	11.6	9.1	9.6	
110	5.9	6.9	7.9	6.0	7.4	4.5	6.4	7.9	7.6	7.7	8.9	8.5	8.0	10.4	8.5	8.9
111	6.6	6.3	6.7	5.4	7.1	4.6	6.1	±2.8	7.7	7.4	5.7	8.9	11.7	7.4	8.1	± 3.4
112	8.3	9.6	15.0	8.0	12.8	9.3	10.5		10.5	12.6	13.8	13.6	13.9	12.3	12.8	
									During 6 Days on a High (600 g man^{-1} day^{-1}) COH Intake							
121	11.3	8.5	9.9	9.4	10.1	11.4	10.1		10.6	9.3	11.6	12.3	12.5	13.4	11.6	
122	6.7	7.7	7.2	8.5	7.5	8.1	7.6		9.4	11.6	11.3	12.5	10.7	12.4	11.3	
123	14.6	11.2	11.6	11.5	12.6	13.9	12.6		12.1	14.1	15.4	14.7	14.0	12.6	13.8	
124	10.8	9.8	9.6	8.9	7.7	10.4	9.5		13.3	14.6	12.8	14.7	8.6	8.8	12.1	
126	7.7	10.1	8.3	9.4	7.0	9.3	8.6	9.1	10.7	13.9	12.6	9.4	12.3	14.4	12.2	11.6
129	8.6	10.1	7.3	11.2	10.2	11.5	9.8	±2.3	12.1	10.4	12.0	12.4	14.7	13.2	12.5	± 2.4
130	4.3	6.5	4.2	5.5	5.5	7.0	5.5		7.6	9.9	7.6	8.2	6.5	5.9	7.6	

the NCD or the HCD, 92 of 808 urine specimens (11.4%) voided during the first 6 days of this regime had calcium concentrations higher than 9 mmol/l (Fig. 2). There is a highly significant difference in the results between these 2 dietary regimes.

Graphs were made of the calcium concentration in sequential urines passed by 6 subjects during the second week of taking the LCD (Fig. 3) and during the first week of taking the higher carbohydrate regimes (NCD or HCD) (Fig. 4).On the LCD, urine calcium concentration, whilst varying throughout the day and achieving peaks mostly in the middle of the day, exceeded 9 mmol/l in only 2 of the subjects (Subjects 12 and 23). On higher carbohydrate regimes the upper limit of calcium concentration of 9 mmol/l was exceeded by all subjects on several occasions during a 6-day period and the peaks of calcium concentration throughout were more frequent and of greater amplitude.

Discussion

The analysis of large numbers of individual urine specimens in this study has revealed the profound diurnal variation in calcium excretion rate in the majority of normal subjects. When this is compared with the results of analysis of 24-h collections in the same subjects, it is clear that the latter conceal the number, frequency and height of peaks of calcium concentration which occur throughout the day. The finding of "normal" excretion rates of calcium in 24-h urine collections during the metabolic assessment of calcium oxalate stone formers, therefore, does not exclude a propensity to produce high concentrations of urinary calcium during the diurnal phase of excretion, and this can account for the large proportion of such patients who are described as showing no metabolic abnormality. The further evaluation of the results of this and other planned studies may indicate a

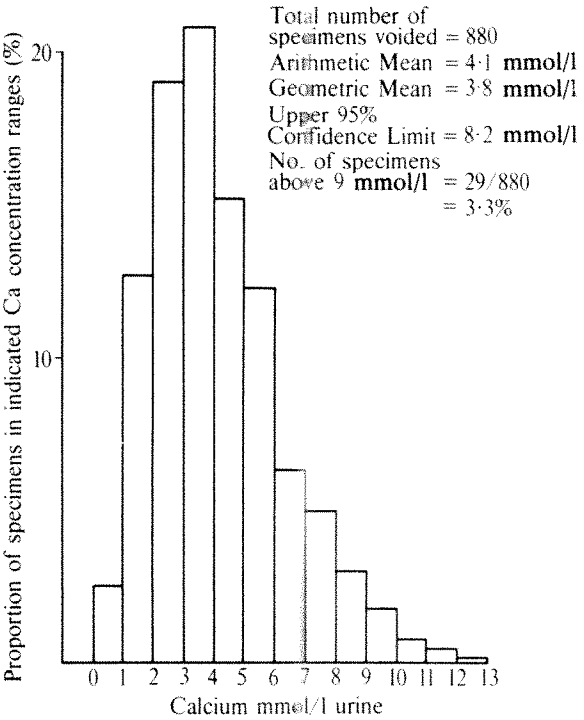

Fig. 1 Range of calcium concentration in individual urines from 19 young men during the second week on the standard diet containing 200 g of available carbohydrate (LCD).

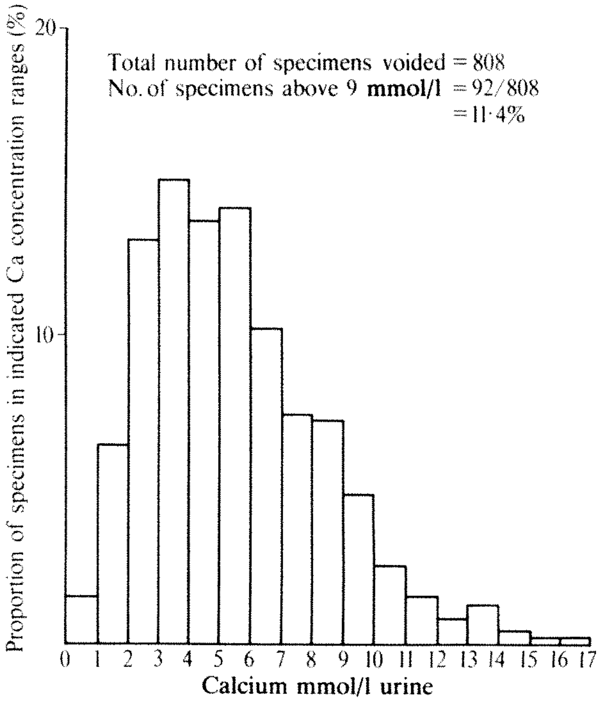

Fig. 2 Range of calcium concentration in individual urines from 18 subjects during the first 6 days on a standard diet containing 400 (NCD) or 600 g (HCD) available carbohydrate.

more satisfactory screening test in this disease.

Evaluation of the pattern of calcium excretion in this study has shown a tendency for maximum calcium concentration in the urine to take place during the day and it is significant that urine oxalate excretion is maximal at the same time (Hargreave *et al.*, 1977). There is, therefore, a risk at this time of the formation product of calcium oxalate being exceeded.

The higher amplitude of peaks of calcium concentration shown by some normal subjects in this study, *e.g.* subjects 12 and 23 (Fig. 3), suggest a sub-group of individuals in whom there is a spontaneously greater risk of the urine exceeding the formation product of calcium oxalate, whilst at the same time showing normal rates of calcium excretion in 24-h collections.

Lastly, the study has shown that in addition to the known acute effect of a sugar bolus on urinary calcium excretion, normal dietary supplements of refined carbohydrate will significantly increase the number and magnitude of peaks of urinary calcium concentration even in normal subjects when compared with the urinary profile on a diet with lower refined carbohydrate content. Since these peaks occurred at a time when oxalate excretion is also maximal (Hargreave *et al.*, 1977), there is the likelihood that a dietary structure which includes significant amounts of sugar or sugar products will increase the risk of the formation product of calcium oxalate being exceeded. In showing that dietary structure can influence the urinary electrolyte profile towards greater supersaturation with calcium oxalate, this study provides a link between diet and the rate of idiopathic calcium stone formation, fulfilling one of the requirements of Andersen's hypothesis (Andersen, 1972).

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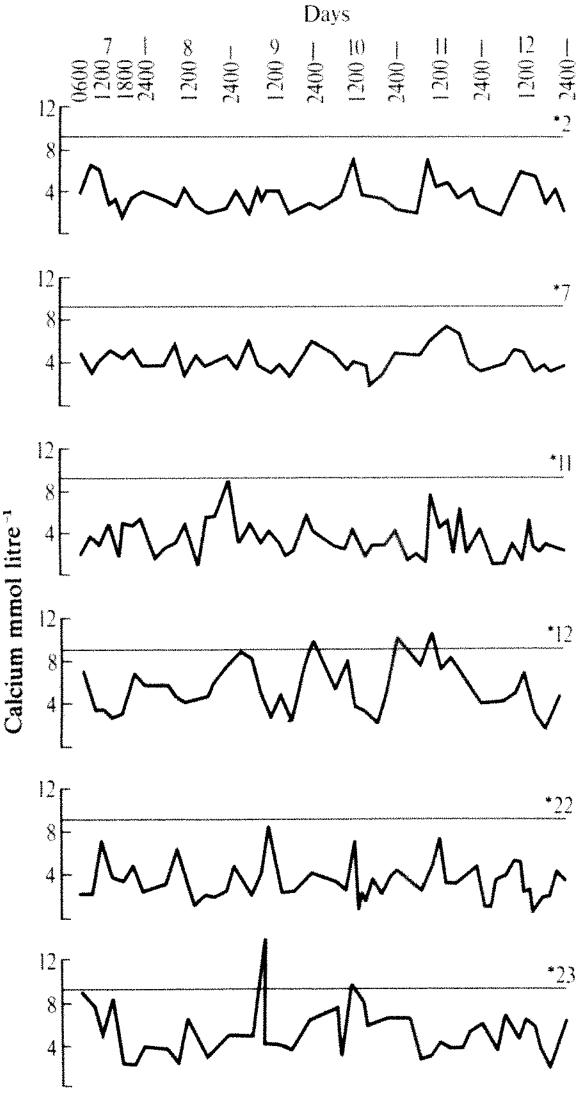

Fig. 3 Diurnal variation in urine calcium concentration in individual urines voided by 6 normal subjects during the second week of a standard diet containing 200 g of available carbohydrate (LCD).

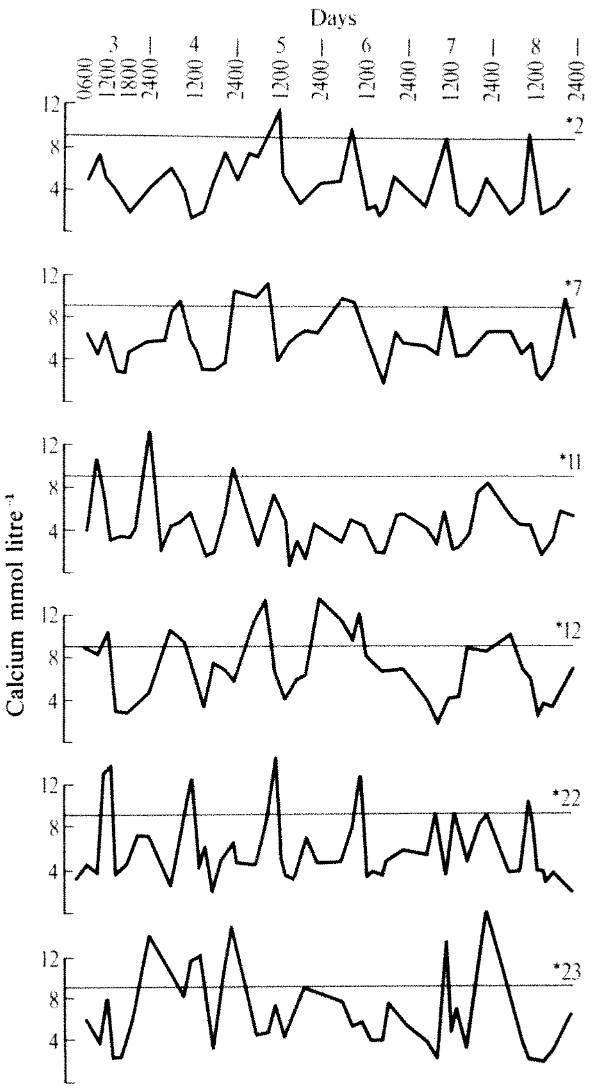

Fig. 4 Diurnal variation in calcium concentration in individual urine specimens voided by the same 6 normal subjects as in Fig. 3 during the first week of a standard diet containing 400 g available carbohydrate (NCD) in the case of subjects 2, 7, 11 and 12 and 600 g available carbohydrate (HCD) in subjects 22 and 23.

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Inosine: Clinical Results of Ischaemic Renal Surgery

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Summary—Ten patients requiring ischaemic renal surgery for calculus or tumour were operated on with the kidney protected by perfusion with a room temperature solution of inosine. The warm ischaemic times ranged from 35 to 75 min (mean 57.1 min).

Post-operative recovery was uneventful in all patients. No adverse cardiodynamic effects due to inosine were noted. There was only moderate transient depression in renal function as assessed by gamma camera renography and serum creatinine estimations. Three of the 10 patients have now been followed for over a year. The results with inosine perfusion are comparable to those obtained with hypothermic protection.

Preservation of the kidney during prolonged periods of ischaemia is essential in ischaemic renal surgery and renal transplantation. Preservation has hitherto been achieved mainly by the use of hypothermia.

In a study in rats of methods of counteracting ischaemic renal injury (after an initial period of warm ischaemia by perfusing the *in situ* kidney with various perfusates in comparison with isotonic saline or blood) the best results were obtained with autologous arterial blood perfusion. Results with commonly used perfusate solutions were no better than in controls irrespective of whether the perfusate was at 4°C or 37°C. Results after perfusion with isotonic saline at 37°C appeared to be better than in controls during the limited period of ischaemia used (Fernando *et al.*, 1977c).

Further experiments were done where purine nucleotides and nucleosides and other substances were used as pre-treatment or at commencement of the period of warm ischaemia with the aim of providing metabolic support to a failing kidney (Fernando *et al.*, 1976). In these studies the purine nucleoside inosine was found to be effective in protecting the kidney during a one-hour period of warm ischaemia as regards plasma creatinine and survival after ischaemia. Moreover, during ischaemia, inosine-perfused kidneys maintained higher total levels of inosine monophosphate (IMP), adenosine monophosphate (AMP) and adenosine diphosphate (ADP) than controls, and on restoration of blood flow the inosine-protected kidneys rapidly regained normal tissue levels of adenosine triphosphate (ATP).

Experiments were repeated in dogs and again plasma creatinine after inosine perfusion and 60 min ischaemia at 37°C was significantly lower than in controls and terminal (7th day) creatinine clearances were significantly higher than in the controls and not different from the clearance in the normal kidney (Fernando *et al.*, 1977 a).

The enzyme gamma glutamyl transpeptidase (γ-GT) is located in the highest concentration in the renal tubular brush border and its excretion in the urine is a sensitive indicator of ischaemic renal damage (Ward, 1975). With 90 min of renal ischaemia at 37°C in dogs, urinary γ-GT excretion was minimal when the kidney was protected by inosine perfusion. This evidence indicated that inosine might protect the proximal brush border and this has been confirmed by electron microscopy.

In view of the success of these experiments, clinical evaluation of inosine was undertaken in patients requiring renal surgery for removal of stones or tumours in a bloodless field. A pharmaceutically available preparation of inosine (Linquette *et al.*, 1967) was used after initial evaluation in animal experiments.

The clinical results are presented in this paper.

Patients and Methods

In 10 patients aged 24 to 74 years (mean 46.9 years) with renal calculus or tumour (Table) the

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Read at the 34th Annual Meeting of the British Association of Urological Surgeons in Brighton, June 1978.

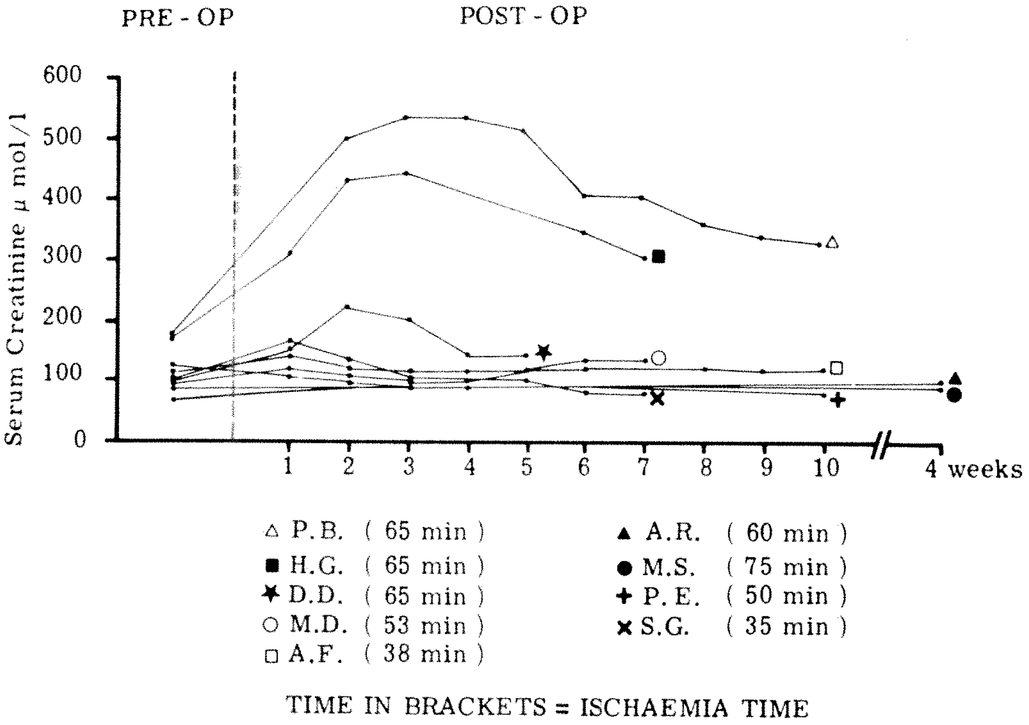

Fig. 1 Serum creatinine before and after operation.

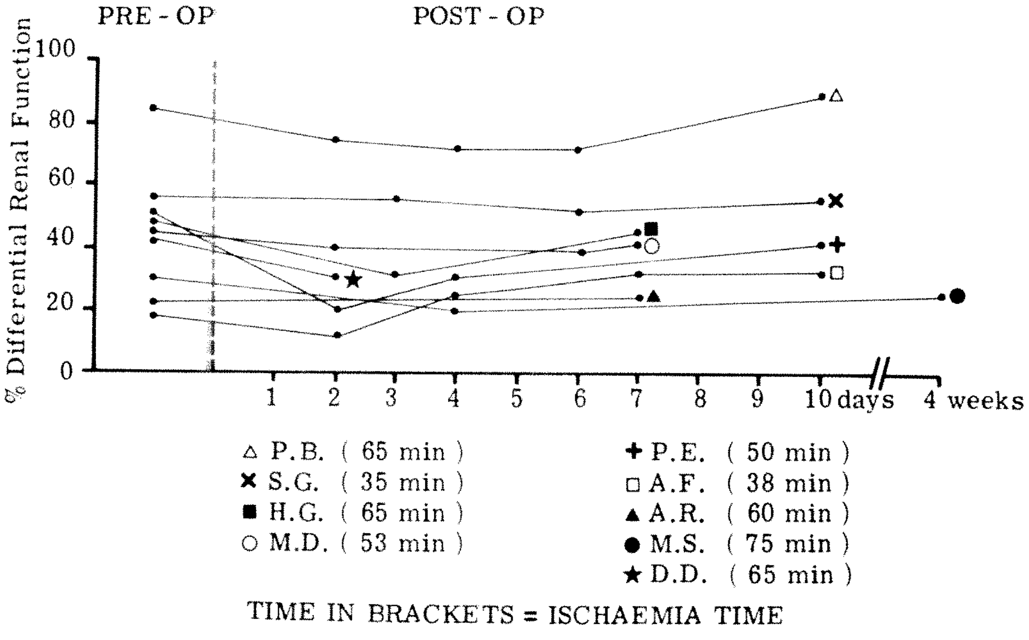

Fig. 2 Percentage contribution of the operated kidney to total renal function (gamma camera renography) before and after operation.

Table

Case	*Age (Yr)*	*Sex*	*Operative Procedure*	*Ischaemia Time (min)*
A.R.	24	Male	Rt pyelonephrolithotomy	60
P.B.	33	Female	Lt nephrolithotomy	65
A.F.	49	Female	Rt nephrolithotomy	38
P.E.	40	Female	Rt pyelolithotomy	50
S.G.	75	Male	Excision of rt renal tumour	35
M.S.	25	Female	Lt nephrolithotomy	75
H.G.	59	Male	Lt nephrolithotomy	65
D.D.	59	Female	Rt pyelonephrolithotomy	65
M.D.	57	Female	Lt nephrolithotomy	53
A.V.	48	Female	Lt nephrolithotomy	65

kidney was exposed through an oblique loin incision or a lumbotomy incision (Ward *et al*., 1976). The kidney was mobilised, the renal artery isolated and occluded with a small bulldog clamp. A fine cannula was inserted into the renal artery distal to the clamp and the kidney perfused with 80 ml of a room temperature solution containing 2 g inosine (Trophicardyl, Laboratoire Chantereau, Arcueil, Paris). The renal vein was then occluded with a second bulldog clamp. On completion of the operative procedure the clamps were removed.

Renal function was measured pre-operatively and post-operatively with repeated serum creatinine estimations, and differential renal function was assessed by gamma camera renography. Results in one patient are incomplete.

Results

The period of ischaemia ranged from 35 to 75 min (Table) with a mean of 57.1 min. No adverse cardiodynamic effects were noted following inosine perfusion of the kidney. All patients had an uneventful post-operative course.

Serum creatinine and differential function on renography are shown in Figure 1 and Figure 2 respectively. Minimal to moderate elevations in creatinine returned to normal within 7 days in most cases. The percentage contribution to total renal function of the operated kidney was virtually unaltered as assessed by radioisotope renography.

A transient elevation of serum uric acid was seen in some patients.

All patients are well and have been followed up for periods ranging from 2 months to 1 year.

Discussion

The clinical results with inosine are highly encouraging and similar to the results in patients operated upon with hypothermic protection during comparable ischaemia times (Wickham *et al*., 1974). The inosine technique is simpler than hypothermia insofar as additional bulky equipment is not necessary. Puncture of the renal artery involved in inosine perfusion, however, may be a disadvantage, though so far we have not encountered any complications.

Further studies are continuing on the use of inosine in cadaver kidney retrieval and preservation and on its use for more prolonged periods of ischaemia. Already intravenous inosine has been found to afford protection for up to 120 min warm ischaemia in the rat (Fernando *et al*., 1977 b).

In the light of present knowledge, the ischaemic period for clinical use with inosine protection should not exceed 1 h or, at the most, 1 h 15 min.

Acknowledgements

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Pre-operative Arterial Embolisation in Renal Carcinoma

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Summary—Nephrectomy for carcinoma is often accompanied by moderate or severe bleeding but this may be reduced by prior occlusion of the renal artery.

Embolisation with fresh autologous clot is rendered ineffective by rapid lysis.

In vitro experiments showed that the clot could be stabilised by the addition of epsilon amino caproic acid (EACA).

By injecting stabilised clot into the renal artery, satisfactory devascularisation of kidney and tumour was achieved in 10 patients.

A number of techniques have been developed for the purpose of arresting the renal circulation prior to nephrectomy for tumour. Marberger and Georgi (1975) used a balloon catheter to occlude the lumen of the artery. Almgard *et al.* (1973) injected muscle into the artery while Paster *et al.* (1975) and Ben-Menachem *et al.* (1975) employed gelatine sponge in a similar manner. More dramatically, Turner *et al.* (1975) used a ferrous-silicone compound held in position by a magnetic field. Injection of untreated fresh autologous blood clot is unsatisfactory because the clot rapidly undergoes lysis. Silber *et al.* (1976) have taken advantage of the rapidity of natural lysis to employ renal artery injection of clot in the treatment of haemorrhage caused by renal trauma. In one case of renal tumour we injected the renal artery with untreated autologous blood clot, but at operation 48 h later the blood supply of the tumour was unimpaired and appreciable blood loss resulted. It was decided, therefore, to carry out experiments to discover a satisfactory way of stabilising the blood clot and, having done so, to apply the technique to the treatment of patients with carcinoma of the kidney.

Patients and Methods

In vitro *Experiments*

Blood clot in the circulation is rapidly lysed by the fibrinolytic system. Various fibrinolytic inhibitors have been used to prevent this process. In an attempt to find a simple method of temporarily preventing lysis *in vitro*, various antifibrinolytic agents in different concentrations were incubated at room temperature with whole blood, and the degree of lysis studied.

Epsilon amino caproic acid (EACA), aprotinin (Trasylol) and tranexamic acid were mixed with whole blood in varying concentrations. For the purpose of this experiment lysis was graded visually.

As can be seen from the accompanying chart (Table 1) the most effective combination for resisting lysis appeared to be whole blood mixed with 1:5 dilution of EACA. The clot thus obtained was remarkably stable even after 10 days. The addition of a small amount of thrombin appeared to increase the stability. Surprisingly, tranexamic acid, theoretically a more potent antifibrinolytic agent, did not appear to be superior to EACA.

Clinical Experience

Renal embolisation using autologous blood clot and EACA was carried out in 10 patients with malignant tumours. Pre-operative assessment of patients included routine blood screening (full blood count, ESR, biochemical profile and transaminase estimation), an intravenous urogram, chest X-ray and urine culture. A glucoheptonate isotope renal scan was performed to determine the site of the lesion and a pertechnetate renal perfusion scan to assess blood flow through the tumour. Retrograde catheterisation of the abdominal aorta through the femoral artery was carried out by the Seldinger technique. Fifty millilitres of blood were withdrawn and mixed

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Table 1 Results of Experiments to Determine Stabilising Effect of EACA, Trasylol and Tranexamic Acid on Blood Clot

EACA 0.4 g/ml	*Days*					
	1	*3*	*5*	*7*	*10*	*14*
Blood alone	+	+ + +	+ + +	+ + + +	+ + + +	
Blood + EACA 1/10	—	—	+	+	+ +	+ +
Blood + EACA 1/10 + 1 drop thrombin	—	—	+	+	+	+ +
Blood + EACA 1/10 + 1 drop fibrinogen	—	—	+	+	+ +	+ +
Blood + EACA 1/5	—	—	—	—	—	+
Blood + EACA 1/5 + 1 drop thrombin	—	—	—	—	—	—
Blood + EACA 1/5 + 1 drop fibrinogen	—	—	—	—	+	+
Trasylol 5000 KIU/ml						
Trasylol 1/10	—	+	+ +	+ +	+ + +	+ + + +
Trasylol 1/10 + 1 drop thrombin	—	+	+ +	+ + +	+ + +	+ + + +
Trasylol 1/10 + 1 drop fibrinogen	—	+	+ +	+ +	+ +	+ + +
Trasylol 1/5	—	+	+ +	+ + +	+ + +	+ + +
Trasylol 1/5 + 1 drop thrombin	—	+	+	+ +	+ + +	+ + +
Trasylol 1/5 + 1 drop fibrinogen	—	+	+	+ +	+ + +	+ + +
Tranexamic Acid 100 mg/ml						
Blood + tranexamic acid 1/10	—	+	+	+	+ +	+ +
Blood + tranexamic acid 1/10 + 1 drop thrombin	—	+	+	+	+ +	+ +
Blood + tranexamic acid 1/10 + 1 drop fibrinogen	—	+	+	+	+ +	+ +
Blood + tranexamic acid 1/5	—	+ +	+ +	+ +	+ +	+ + +
Blood + tranexamic acid 1/5 + 1 drop thrombin	—	+ +	+ +	+ +	+ +	+ + +
Blood + tranexamic acid 1/5 + 1 drop fibrinogen	—	+	+	+ +	+ +	+ +

Grading of lysis
— No lysis
+ Mild clot retraction
+ + Moderate clot retraction
+ + + Marked clot retraction
+ + + + Complete lysis of the clot.

with 10 ml of EACA (0.4 g/ml) in a glass container. Following a mid-stream aortogram the catheter was changed for a red pre-formed Kifa catheter and a selective renal angiogram performed. The Kifa catheter was then advanced as far as possible into the renal artery. The syringe was filled with the treated blood clot which, although of a firm rubbery consistency, nonetheless injected easily. The clot was injected under screen control followed by small volumes of contrast to assess the degree of occlusion (Figs. 1 and 2). The volume of clot required varied from 10 to 25 ml. Occlusion was complete when contrast failed to clear from the renal artery and the excess refluxed freely into the aorta. Loin discomfort was usually experienced. Following embolisation development of pain was noted and judged as being severe (requiring 100 mg of intramuscular Pethidine), moderate, mild or absent. Pulse and temperature charts were maintained and the serum transaminase estimated daily.

The renal perfusion scan was repeated after 24 h to assess residual blood flow through the tumour and nephrectomy was carried out within 48 h of embolisation, with the exception of Case 2 where the procedure was performed as a palliative form of treatment to control haematuria.

Results

Five patients complained of severe loin pain which settled within 12 h following intramuscular Pethidine (Table 2). The remaining 5 patients felt a mild or moderate degree of pain. The follow-up renal isotope perfusion scans confirmed reduction in the tumour blood flow in all cases studied. Serum transaminase levels were elevated

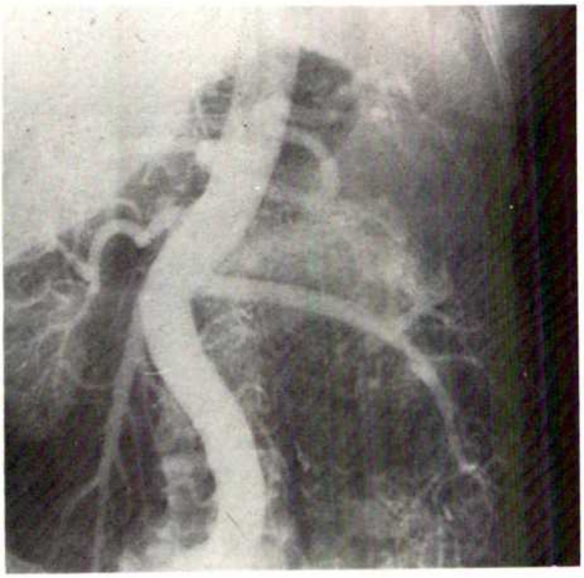

Fig. 1 Case 1. Mainstream aortogram showing highly vascular tumour of left kidney.

within 12 h following the procedure. In 3 patients who presented with large palpable masses, the tumours became significantly smaller on examination following embolisation.

In each case the kidney and its tumour appeared ischaemic at operation and the large veins in the perinephric tissue, so often responsible for severe haemorrhage, were collapsed and did not bleed appreciably on division. A zone of oedema surrounded the tumour and facilitated dissection. The main renal artery, however, remained pulsatile and this unexpected finding aided its localisation within the renal pedicle. Blood loss during the operation was minimal and although one case received one unit of blood this was judged in retrospect to have been unnecessary.

Dissection of the operation specimens confirmed widespread thrombosis in the arterial tree and ischaemic changes in the kidneys and tumours. Histological examination of the specimens confirmed typical renal carcinoma. Some of the major arteries contained thrombus and the renal parenchyma revealed areas of infarction. The patient who underwent embolisation as a palliative procedure (Case 2) remained well at 2 months with no recurrence of haematuria and repeat renal perfusion scans confirmed that the reduction in tumour blood supply was maintained. However, after another 2 months she complained of troublesome loin pain and despite angiographic evidence of metastases in the opposite suprarenal region, nephrectomy was advised and performed.

Discussion

Nephrectomy for renal carcinoma is always associated with some blood loss and sometimes this may be quite severe. The increased blood supply to the organ and its contained tumour, and the presence of arteriovenous anastomoses within the tumour, give rise to an elevated pressure in the veins surrounding the organ which in turn become varicose and bleed freely on division. Their friability makes ligation difficult or impossible. The bleeding will continue until the renal artery is ligated, when pressure falls, bleeding becomes minimal and the kidney and tumour shrink. It is unfortunate that in some accounts of the operation stress is laid on the prior ligation of the renal vein. When this advise is followed the result is aggravation of the bleeding with swelling of the tumour, and the operation becomes increasingly difficult. On the contrary, the aim of the surgeon should be to ligate the artery at the first opportunity, but this may entail considerable dissection during which time haemorrhage continues. Our experience

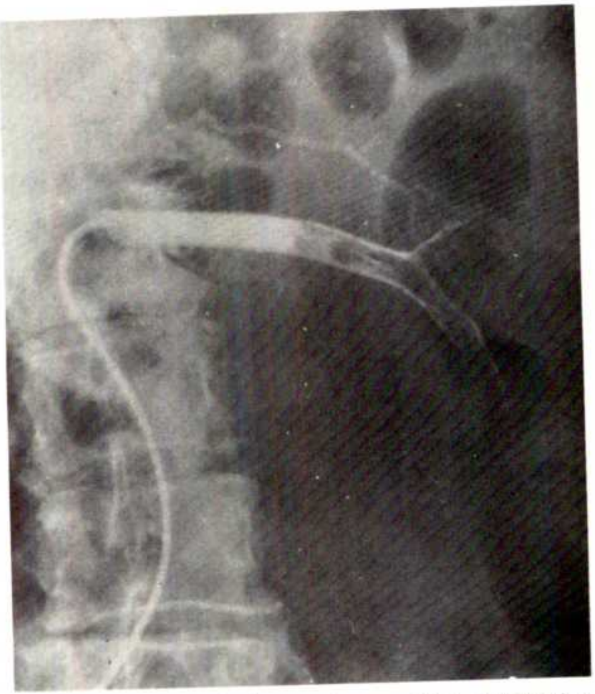

Fig. 2 Case 1. Selective angiogram after embolisation showing devascularisation.

Table 2 Results of Renal Embolisation with Blood Clot Treated with EACA in 10 Cases of Renal Carcinoma

Patient	*Sex*	*Age*	*Side of lesion*	*Embolisation: Vol. of clot and EACA*	*Loin pain*	*Peak transaminase (LDH) level (units/litre)*
1. G.L.	F	75	L	15 ml	Severe	—
2. D.B.	F	62	L	20 ml + Gelfoam	Moderate	2760
3. B.K.	F	38	R	25 ml	Severe	4275
4. R.F.	M	57	R	10 ml	Severe	3060
5. R.S.	M	62	R	15 ml	Moderate	1200
6. H.L.	M	68	L	15 ml	Mild	1130
7. G.D.	F	70	R	15 ml	Moderate	1470
8. K.D.	M	44	R	20 ml	Severe	510*
9. E.W.	F	62	L	2o ml	Moderate	645†
10. W.V.	M	59	L	14 ml	Severe	1980

* Nephrectomy within 5 h of injection.

† One week after nephrectomy.

confirms that the blood loss can be almost entirely prevented by occluding the renal artery preoperatively. Some of the procedures employed to obtain arterial occlusion are detailed above, but we have found that a simpler technique using autologous blood clot treated with EACA produces excellent control of the arterial blood supply.

To spare the patient the discomfort of 2 angiograms the procedure may be carried out immediately after diagnostic angiography has been performed and it is our experience that if the operation is performed within 2 days of the occlusion, a very satisfactory ischaemia of the kidney and its contained tumour is obtained. Case 1 demonstrated particularly well the advantages of this technique. The patient was a 75-year-old woman in fair condition with a very large left renal tumour. The angiogram (Fig. 1) showed that the lesion was extremely vascular. At operation following embolisation (Fig. 2) the kidney and tumour had shrunk considerably, the veins surrounding the organ were collapsed and an easy nephrectomy was performed without appreciable blood loss.

To avoid blood clot finding its way to the peripheral circulation it is important that the catheter should be inserted well into the renal artery and it may be that the procedure would not be feasible in some cases where there are multiple renal arteries.

It is of interest that although satisfactory occlusion of the artery takes place by this technique, the renal artery remains pulsatile, and this is of great advantage in guiding the surgeon and achieving easy and early ligation of the vessel. However, early ligation of the renal artery, so important in conventional nephrectomy for tumour, becomes less essential when the technique of prior arterial obstruction is employed.

There is clearly a place for this technique in the treatment of inoperable cases of carcinoma of the kidney. Troublesome and persistent haematuria may be arrested and by destroying a large bulk of the tumour immunological benefits may be obtained. In these cases, however, the use of muscle or gelatine sponge may be more appropriate than that of blood clot treated with EACA, or, as in Case 2, the technique may be combined.

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The Management of Vesicoureteric Reflux in Children

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Summary—One hundred and seventy children with vesicoureteric reflux have been reviewed. Conservative therapy was the treatment of choice in Grade I reflux. Children with Grade II and Grade III reflux treated conservatively developed progressive upper tract dilatation and scarring. Unilateral reflux sometimes became bilateral. In addition, the grade of reflux could worsen in the absence of symptoms or overt infection.

Cystourethroscopy was an important investigation as an aid to management: the finding of abnormal ureteric orifices in the presence of Grade II and Grade III reflux indicated early surgical treatment. Surgery was also indicated in the presence of ureteric dilatation on excretion urography and/or micturating cystourography. Vesicoureteric reimplantation gave excellent results, with few complications.

The aetiology, significance and treatment of vesicoureteric reflux in children, despite a considerable volume of literature, still remain controversial. It is well known that reflux is common in childhood whilst relatively rare in adults. Amar *et al.* (1976) stated that vesicoureteric reflux ceases spontaneously after medical management in 55% of children, which compares well with other published results (Williams, 1971; Scott, 1977).

Treatment of vesicoureteric reflux, therefore, varies from conservative for mild cases to surgical for children with severe reflux. However, the majority of children have reflux of an intermediate degree and it is in this group that controversy still exists as to whether they are best treated by conservative or surgical means.

In an effort to try and clarify this confused situation a detailed retrospective study of the management of 170 children with vesicoureteric reflux has been made. The children were all treated in the Department of Paediatric Urology in Bristol and Bath between 1965 and 1977. Whilst some were referred directly to the Department, most were seen in association with our paediatric colleagues.

Patients

There were 123 girls and 47 boys, a female to male ratio of 2.6:1. Their ages at the time of presentation are shown in the Figure. It is interesting that only just over half of the children had had symptoms for less than 1 year (Table 1).

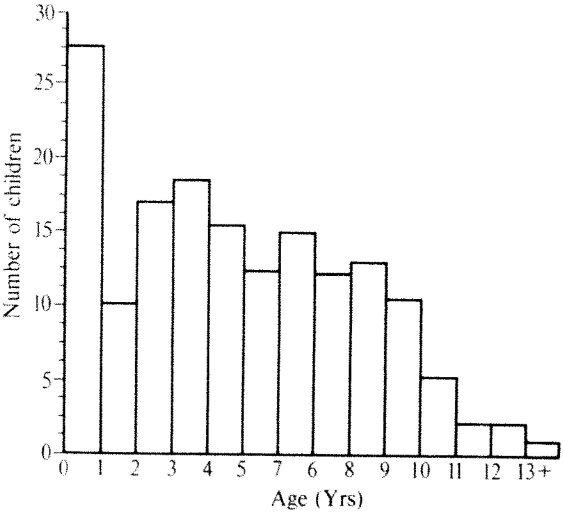

Fig. Reflux in Children: Age Incidence

Table 1 Length of History

Acute Illness	25
Less than 6 months	37
6 months–1 year	24
1 year–2 years	19
2 years–3 years	16
Greater than 3 years	38
Not specified	11
Total	170

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The commonest presenting symptoms were those of lower urinary infection (frequency, dysuria, and suprapubic discomfort) and in the younger children either febrile convulsions or febrile illnesses. Sixty-one patients complained specifically of pain and this tended to be generalised abdominal pain in the younger children and loin pain in the older children (Table 2).

Table 2 Presenting Symptoms

Lower urinary tract symptoms	83
Pyrexial illnesses	61
Enuresis	42
Abdominal pain	31
Loin pain	30
Malaise	27
Day time incontinence	22
Febrile convulsion	15
Tiredness	13
Painful haematuria	11
Smelly/"cloudy" urine	11
Failure to thrive	8
Retention of urine	4
Chance finding	3
Septicaemia	1
Polyuria/polydypsia	1
Prolapsed ectopic ureterocoele	1

In only 23 patients was the urine sterile on presentation but many of these children were already on antibiotic therapy. *E. coli* was the responsible organism in 94 children with infection (Table 3).

Table 3 Urine Culture on Presentation

Urine sterile	23
Significant infection	
E. Coli	94
Proteus	10
Streptococcus faecalis	3
Pseudomonas	2
Klebsiella	1
Organism not specified	37
Total	170

At presentation or referral a full history was taken and complete clinical examination performed. Investigations included microscopy and culture of a mid-stream specimen of urine, excretion urography and micturating cystourethrography; in some patients cystourethroscopy was also performed.

Excretion urography was normal in 53 children; cortical scarring and/or caliceal clubbing indicating reflux nephropathy was present in 69. Dilatation of the upper tracts was present in 91 children. Upper tract duplication was present in 24 children (Table 4). Vesicoureteric reflux has been graded as follows:

Table 4 Initial Excretion Urography

Normal		53
Dilated upper tracts		65
Upper tract duplication		24
Reflux nephropathy		
Bilateral		13
Unilateral	Right	25
	Left	26
Non-function		5

Grade I. Reflux into ureter only, with no dilatation.

Grade II. Reflux reaching the pelvicaliceal system, with no dilatation.

Grade III. Reflux into ureter and/or pelvicaliceal system, with dilatation.

The findings of the initial micturating cystogram are shown in Table 5. The small number of children with Grade I vesicoureteric reflux almost certainly reflects the fact that most of the children were referred by paediatricians and it would seem likely that many of the milder cases were never referred.

Table 5 Initial Micturating Cystourethrography

Vesico-ureteric Reflux	*Left*	*Right*	*Bilateral*	*No. of units*
Grade I	10	6	0	16
Grade II	14	17	7	45
Grade III	42	30	44	160

In 81 children a cystoscopy was performed. This was done prior to surgery both in the assessment of reflux and to identify any associated bladder abnormalities (Table 6).

Treatment

One hundred and thirty-four children (79%) have been initially treated conservatively on a regime of multiple micturition and a prolonged course of antibiotic therapy. Ninety-six children were considered to have failed on this regime because of recurrent symptoms, recurrent infections, worsening of the grade of reflux or progressive changes in the upper tracts as shown by excretion urography.

Table 6 Cystoscopic Findings

Normal —13		
Abnormal—68		
Patulous ureteric orifices	Right	15 (lateralised 2)
	Left	21 (lateralised 5)
	Bilateral	17 (lateralised 1)
Trabeculation	42	
Tight urethra	6	
Paraureteric diverticulum	5	
Raised bladder neck	4	
Chronic cystitis	4	
Ectopic ureterocoele	4	
Urethral valves	2	
Bladder stone	1	

Table 7 Changes in Vesicoureteric Reflux during Conservative Treatment

Before treatment		*After treatment*	
Degree of reflux	*No. of patients*	*Degree of reflux*	*No. of patients*
		Nil	4
Grade I	6	Grade I	1
		Grade II	0
		Grade III	
		Nil	8
Grade II	14	Grade I	2
		Grade II	3
		Grade III	1
		Nil	4
Grade III	16	Grade I	1
		Grade II	5
		Grade III	6
Total patients 36			

Thirty-six children are still being managed on a conservative regime, as well as 2 children with vesicoureteric reflux who have had urethral valves destroyed endoscopically.

Thirty-two children had vesicoureteric reimplantation as the initial treatment. Three had cutaneous ureterostomy followed by vesicoureteric reimplantation at a later stage, and one had a nephroureterectomy. This makes a total of 36 children (21%) who were treated surgically in the first instance.

Conservative Treatment

Of the 36 children who were managed conservatively, 6 had Grade I, 14 Grade II and 16 Grade III reflux. The period of conservative treatment varied from 3 months to 6 years (mean 2.75 years). Twenty-three had no symptoms, 7 had occasional symptoms, whilst 4 had recurrent symptoms of urinary tract infection, and in 2 children no details of symptoms were given. The urine was sterile in 25, infected in 6 children, and not known in 5 children.

Excretion urography, after a period of conservative management, remained normal in 17 children. In no children did normal urography become abnormal, whilst in 2 upper tract dilatation improved.

The changes in the degree of reflux following conservative treatment are shown in Table 7.

Surgical Treatment

One hundred and thirty-one children have been treated surgically for vesicoureteric reflux by ureteric reimplantation, whilst one had a primary nephroureterectomy.

Conservative treatment was used initially in 96 of these children but failed to control either symptoms, infection, grade of reflux or prevent progressive changes in the upper tracts as seen on excretion urography. The period of conservative treatment varied from 6 weeks to 11 years (mean 2.8 years). The changes shown on excretion urography during conservative therapy are shown in Table 8.

Table 8 Changes on Excretion Urography following failed Conservative treatment

Normal pre-treatment	
Normal Post-Treatment	24
Normal pre-treatment	
Abnormal Post-Treatment	
(a) Dilatation	2
(b) Scarring	11
Abnormal pre-treatment	
Abnormal Post-Treatment	
(a) No change	25
(b) Worse dilatation	13
(b) Worse scarring	6
(c) Improved	0
Abnormal pre-treatment	
Normal Post-Treatment	
(a) Dilatation	3
(b) Scarring	0
No post-treatment Urogram	12
Total	96

Twelve children in this group, in whom initially the reflux was unilateral, developed bilateral reflux (1 Grade I, 5 Grade II and 6 Grade III). Table 9 demonstrates the effect of the conservative regime on reflux.

Table 9 Changes in Vesicoureteric Reflux after Failed Conservative Treatment

Before treatment		*After treatment*	
Degree of Reflux	*No. of Patients*	*Degree of Reflux*	*No. of Patients*
		Nil	3
Grade I	9	Grade I	4
		Grade II	1
		Grade III	1
		Nil	1
Grade II	22	Grade I	1
		Grade II	9
		Grade III	11
		Nil	0
Grade III	67	Grade I	0
		Grade II	3
		Grade III	64

Thirty-five children have been treated surgically with no initial period of conservative therapy. Thirty-two had primary vesicoureteric reimplantation and 3 cutaneous ureterostomy followed by reimplantation.

Seventy-three children had bilateral reimplantation whilst 58 had unilateral reimplantation, making a total of 204 reimplantations. The follow-up period ranged from 6 months to 12 years (mean 3.8 years). One hundred children (76%) became symptom-free, 25 (19%) symptomatically improved, whilst 6 (5%) remained symptomatically unchanged. Contralateral reflux has occurred post-operatively in 7 children. Reflux persisted in 5 ureters (2.4%), persisted but improved in 3, and remained unchanged in 2. Four children developed an obstructed ureter post-operatively, needing re-exploration; 3 children subsequently had nephrectomy for non-functioning kidneys.

No further episodes of infection occurred in 94 children (72%). Infection occurred less frequently in 28 (21%) and remained unchanged in 9 (7%).

Discussion

The aetiology and management of vesicoureteric reflux remain somewhat controversial. Primary reflux is considered a congenital defect of the ureterovesical junction and is the most common type. Reflux due to infection and secondary reflux associated with bladder outlet obstruction, neuropathic bladder and ureteric ectopia are important but less common causes (King *et al.*, 1968).

Initially, the changes in reflux nephropathy were attributed to the hydrodynamic effect of reflux but no good evidence has substantiated this belief (Johnston, 1968). Further experimental evidence and clinical experience have shown that vesicoureteric reflux alone does not produce anatomical or functional renal damage (King and Sellards, 1971; King *et al.*, 1974).

It would seem, therefore, that by controlling infection in these children with reflux by prolonged courses of antibiotics, their kidneys would be protected from damage, and eventually reflux would cease. Based on this evidence over the past 12 years, the Department of Paediatric Urology has approached vesicoureteric reflux conservatively.

It is clear from the results of this study that Grade I reflux is easily controlled by conservative means, as are approximately half of the patients with Grade II reflux.

Ninety-six out of 134 children (72%) who had initially been treated conservatively have now undergone antireflux surgery because of either persisting symptoms, persisting infection in spite of continuous antibiotic therapy, no change or worsening of vesicoureteric reflux, or progressive changes, e.g. dilation of the upper tract and/or reflux therapy. Thirteen children in this group had normal excretion urograms at the time of diagnosis but by the time the conservative regime was considered to have failed, 2 had upper tract dilation and 11 had changes of reflux nephropathy. This was in spite of continuous antibiotic therapy.

In a further 19 children with upper tract dilatation or scarring on initial excretion urography, after a period of conservative treatment, progression was noted on repeat urography.

It is possible that these kidneys were damaged initially but it is not until after a period of several years that differential growth in the kidney reveals the scarred areas. It is equally possible that these children forgot to take their medicine and further infection developed with minimal or no symptoms. Finally, it is also possible that persistent reflux in the absence of infection would produce these changes, although this contradicts recent animal work (Ransley and Risdon, 1974).

It would seem clear from this retrospective study that the child with ureteric dilatation on excretion urography and on cystourethrography should be treated surgically. The results of surgery in this series are excellent and compare well with others (Politano, 1963; Amar and Singer, 1973; Scott, 1977).

This series shows a persisting post-operative urinary infection rate of 28%, and is in line with the results of other workers who report a similar incidence varying from 20–36% (Politano, 1963; Jakobsen *et al.*, 1977; Scott, 1977). In addition, it has been found in this series that there has been no development or progression of reflux nephropathy in these children with persisting infection. This finding is in accord with those of Hutch *et al.* (1968) and Dwoskin and Perlmutter (1973).

Cystourethroscopy would appear to be an important investigation making the decision to manage the child conservatively or surgically much easier (Lyon *et al.*, 1969). Thus those children with abnormal ureteric orifices in the presence of Grade II or III reflux should be managed surgically from the outset. In this series, 81 children had cystourethroscopy. The examination in 13 was normal, but in no less than 57 it was possible to demonstrate some abnormality of the ureteric orifice. Cystourethroscopy contributed to the decision on the management of 65 children who had antireflux surgery, and the 16 who continued on a conservative regime.

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The Long-term Follow-up of Surgically Treated Vesicoureteric Reflux

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Summary—We have followed up 83% of a series of 166 patients with vesicoureteric reflux who were treated surgically more than 10 years ago. We found an incidence of hypertension of 12.8%. The need for careful follow-up of the blood pressure of patients with reflux nephropathy is stressed.

The association of vesicoureteric reflux (VUR), urinary infections and pyelonephritic renal scarring is well recognised and the condition has been called reflux nephropathy (Bailey, 1973). Pyelonephritic scarring is the commonest cause of hypertension in childhood (Still and Cottom, 1967; Breckenridge *et al.*, 1968) and is a significant cause of hypertension and renal failure in adults (Rosenheim, 1963).

The incidence of hypertension in treated patients with reflux nephropathy has been estimated at over 11% (Holland *et al.*, 1975; Heale, 1977). In this study we have selected a group of patients who were treated surgically for VUR before 1967 and arranged a simple out-patient follow-up in order to assess the incidence of hypertension and renal failure.

Patients and Methods

A consecutive series of 166 patients who had their first operation for the prevention of vesicoureteric reflux between 1960 and 1967 was selected for study. We excluded all patients who had had previous upper tract surgery and all cases with secondary reflux (mechanical obstruction or neuropathic bladders). Cases of mild bladder neck obstruction diagnosed from the radiology and the presence of a thick walled bladder at operation were included. Patients with duplex systems and paraureteric saccules and diverticula were also included. Their case records were studied to define the clinical features of this series and their management. These patients when traced were asked to attend a reflux follow-up clinic at the Institute of Urology, or they could attend their own doctor or local hospital. Assessment included a history and examination with measurement of the blood pressure standing and lying. The disappearance of the Korotkoff sounds (fifth phase) was recorded as the diastolic blood pressure. A mid-stream specimen of urine was sent for culture and blood was taken for the estimation of plasma creatinine. Further investigations were undertaken only if clinically indicated.

Results

In this series there were 116 girls and 50 boys. The age at onset of urinary infections, duration of infections before operation and age at operation are illustrated in Figures 1, 2 and 3. There were 4 cases which presented with enuresis without documented infections and 3 cases had no well documented evidence of infection.

Renal function was assessed pre-operatively with a creatinine clearance in only 20 patients. All patients had a blood urea estimation. This was above 43 mg/ml (7.0 mmol/l) in 16 patients but all were below 66 mg/100 ml (11 mmol/l). Albuminuria (1 + only) was present in only 4 cases when the urine was not infected.

The blood pressure was recorded pre-operatively in 158 cases (95%). No patients in this series were diagnosed as hypertensive. However, when their blood pressures were compared with those found by the American Task Force on blood pressure control in children (Blumenthal *et al.*, 1977), it was found that 5 patients had both systolic and diastolic blood pressures over the 95th percentile for their age, while 16 patients had a systolic pressure only, and 3 a diastolic pressure only, above the 95th percentile for their age.

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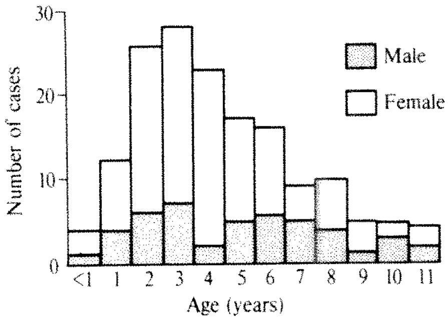

Fig. 1 Age at onset of clinical infections.

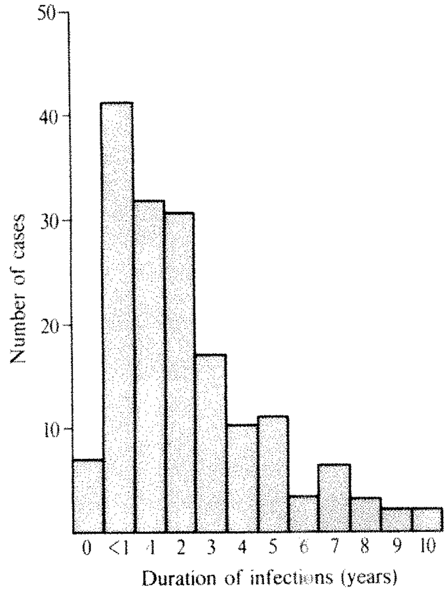

Fig. 2 Duration of infections before operation.

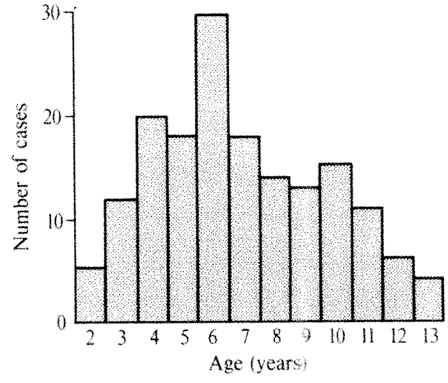

Fig. 3 Age at operation.

In the majority of cases the X-ray reports only were available and it was therefore not possible accurately to quantify the extent of renal parenchymal scarring or the grade of reflux. Table 1 shows the results of the pre-operative IVU according to the presence of renal scarring or upper tract dilatation. There were 92 cases of bilateral reflux and 74 cases of unilateral reflux.

Table 1 Pre-operative Intravenous Urograms

	Total	*Follow-up*
Bilateral renal scarring	43 (26%)	38 (27%)
Unilateral renal scarring	72 (43.3%)	62 (44%)
Dilated collecting systems and normal kidneys	15 (9%)	12 (8.5%)
Normal kidneys and collecting systems	31 (18.7%)	26 (18.5%)
No IVU available	5 (3%)	3 (2%)
	166	141

The surgical procedures performed are given in Table 2. It should be noted that during this period of time a satisfactory technique for ureteric reimplantation was still being evolved (Williams and Eckstein, 1965). The high proportion of patients who also had bladder neck surgery reflects the then accepted view that reflux was frequently a complication of minor degrees of bladder neck obstruction.

Table 2 Anti-reflux Operations 1960–1967

Procedure	*Alone*	*Bladder Neck Myotomy*	*YV Plasty*	*Other*
Hutch	3	12	1	
Bischoff	1	2		
Tunnel and Cuff	19	10	5	
Politano	80	19	5	3
Not Specified	3	2	1	

Follow-up cystograms were obtained at 6 months post-operatively in 158 patients (95%). These showed the presence of reflux in the reimplanted ureter in 24 cases, 8 of which required further surgery to prevent reflux. There were 10 cases which developed contralateral reflux after unilateral reimplantation and only 2 of these cases required further surgery to prevent reflux. In 4 cases the initial post-operative cystogram was negative but reflux was subsequently shown to have recurred.

During the first 5 years of follow-up 44 cases (26%) were shown to have had further urinary infections. Twenty-four patients required a further surgical procedure after their initial reflux prevention. These are listed in Table 3.

Table 3 Further Surgery

For obstruction	Ureteric Reimplants	6
	Ureterolysis	3
For reflux	Ipsilateral	8
	Contralateral	2
For incontinence	Caldwell implant	1
	Bladder neck revision	1
For outflow obstruction	TUR bladder neck	1
Nephrectomy		2
Pyeloplasty		2

The Late Follow-up

One hundred and forty-one cases (85%) were seen and adequately assessed. One hundred and nineteen of these were seen at the Institute of Urology and 22 were seen by their own doctors or by local hospitals. A further 8 cases (5%) were traced but not adequately assessed. Of the 16 that were untraced one had emigrated, and none of the others had been recorded as having died in this country. The mean follow-up period was 13 years with a range of 10–17 years (Fig. 4).

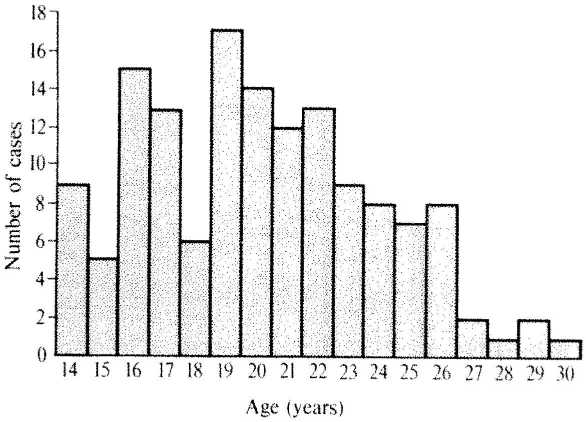

Fig. 4 Age at follow-up.

Blood Pressure

There were 11 cases of hypertension (7.8%) and 7 of mild hypertension (5%). For the purpose of this study we defined hypertension as a blood pressure consistently over 140/90 mmHg and requiring treatment. Mild hypertension was defined as a blood pressure above 140/90 mmHg on more than one occasion but not requiring treatment. Five of the hypertensives and 4 of the mild hypertensives were undiagnosed when they were reviewed. All cases were asymptomatic. The age at which hypertension was detected and the years since surgery are shown in Table 4.

Table 4 Onset of Hypertension

Years Post-op	*Age*
6 months	12
9 years	22
10	17
10	18
10	20
11	18
12	18
13	19
13	20
13	24
15	23
Mean 12 years	Mean 19 years

Two of the hypertensive patients were in renal failure with creatinine clearances of 14 and 13 ml/min respectively. In one case, renal failure preceded the onset of hypertension by one year and in the other case they were diagnosed at the same time. The rest of the patients with hypertension had creatinine clearances at follow-up of between 56 and 171 ml/min/1.73 m^2 (mean 90.5 ml/min/1.73 m^2).

Influence of Renal Scarring

Of the 18 cases with mild and definite hypertension 7 had bilateral renal scarring, 7 had unilateral renal scarring and 3 had normal pre-operative IVUs. One case did not have a pre-operative IVU available.

In the series followed up there were 38 cases with bilateral scarring, giving an incidence of hypertension in this group of 7/38 (18.5%). The incidence of hypertension in those presenting with unilateral renal scarring was 7/62 (11.3%). The 3 patients who had IVUs reported as normal pre-operatively all had abnormalities on their IVUs at 6 months post-operatively. One case had developed bilateral lower ureteric obstruction which required further surgery, while the other 2 had uncomplicated post-operative courses. When the pre-operative systolic blood pressures of the hypertensive patients were compared to the normotensive patients on the percentile charts there did not appear to be a significant difference in their distribution (Fig. 5). However, 4 of the hypertensive patients did not have pre-operative recordings of their blood pressure.

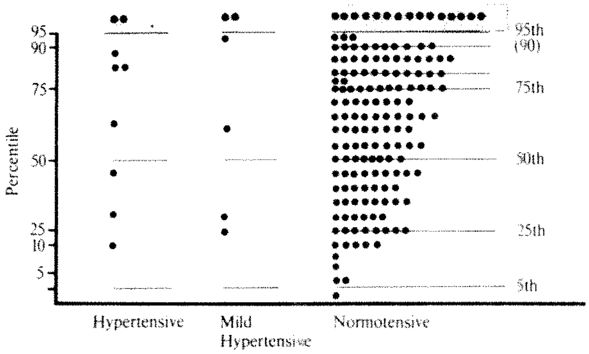

Fig. 5 The pre-operative systolic blood pressures are plotted according to their distribution on the percentile charts and grouped according to their blood pressures on follow-up.

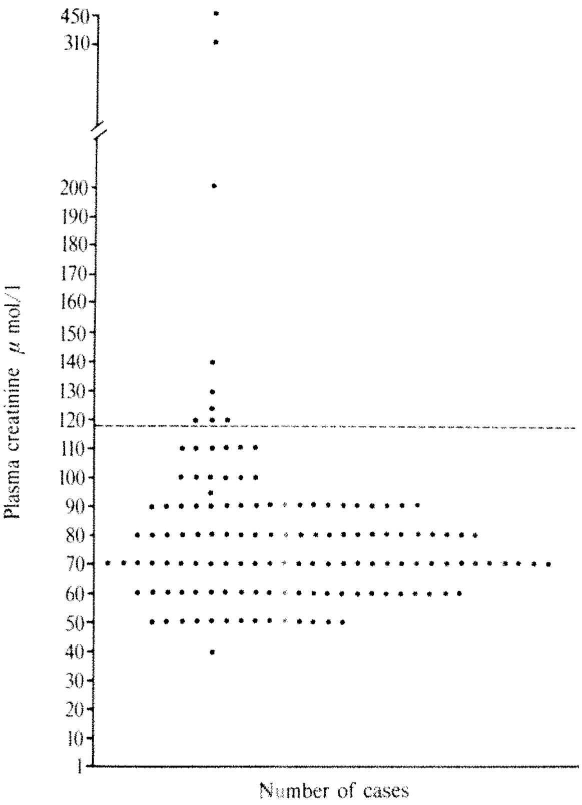

Fig. 6 Results of plasma creatinine on follow-up. See text.

Renal Function

The results of the plasma creatinine are plotted in Figure 6. One normotensive patient as well as the 2 hypertensive patients were in renal failure with a creatinine clearance of less than 20 ml/min. The horizontal line is drawn at 2 standard deviations above the mean value for the third decade.

Infection

Twelve patients gave a history of recurrent urinary tract infection. Twenty patients had had occasional urinary infection (2–5 episodes). All 32 were girls. Only one boy had had an episode of urinary infection. On routine MSU 13 out of 98 girls followed up had significant bacteriuria ($>10^5$ per ml).

Discussion

The incidence of hypertension in adults varies markedly with age and sex. In the Framingham population (Kannel, 1975) there was an incidence of hypertension of 10.3% in men and 2% in women in the age groups 29–34 years. Julius (Julius and Schork, 1971; Julius, 1978) found that 10% of male college students had a blood pressure elevated on more than one occasion. He considered that this condition of borderline hypertension was not benign in view of the significantly increased incidence of future complications. The incidence of hypertension among adolescents and young adults is 1–2.3% (Masland *et al.*, 1956, Londes, 1966).

Our incidence of 7.8% with hypertension severe enough to require treatment is thus greater than expected for this age group (mean 20.3 years, range 14–30 years). The likelihood of developing hypertension is related to the extent of renal scarring (Heale, 1977). Our patients who had bilateral scarring had an incidence of 18.5%. Where scarring was unilateral the incidence was 11.3%. However, 3 patients who had developed hypertension had minimal unilateral renal scarring involving only 1 or 2 calices.

No patient in this series who had a normal IVU 6 months after operation developed hypertension. The development of a renal scar may show up in a DMSA renal scan several months before the scar becomes apparent on an IVU (Merrick, 1978). The pre-operative IVU cannot therefore be relied upon to assess accurately the extent of renal scarring at that time. While the number of patients in this series who had normal kidneys 6 months after operation is small (33 cases), the fact that none has developed hypertension on follow-up suggests that they may not have an increased risk of hypertension.

It is well known that the recording of blood pressure in children, even in specialised units, is frequently omitted (Pazdral *et al.*, 1976). Although 95% of our cases had pre-operative blood pressures recorded as in-patients, when followed up as out-patients this was often omitted. Five of the 11 cases of hypertension requiring treatment were undiagnosed. Thus it is important that where there has been renal scarring the patient, the parents, and hospital and family practitioners should be made aware of the need for the blood pressure to be monitored. The limited significance of isolated recordings of blood pressure is well recognised. It can be seen that our single pre-operative blood pressure recordings bore no relationship to the subsequent development of hypertension (Fig. 5).

At present the extent of renal scarring and the serial measurements of blood pressure are the only guides to the later development of hypertension. In a recent study by Savage *et al.* (1978) 100 normotensive children with reflux nephropathy were studied. Nine were found to have raised plasma renin activities. A longitudinal study is in progress to see if these hyper-reninaemic patients are those who are at risk of subsequently developing hypertension.

No adequately controlled trials of the late results of surgery compared to conservative treatment have been carried out. It will be of interest to note the incidence of hypertension in patients treated conservatively.

Where there is severe unilateral renal scarring the risks of later developing hypertension are high and nephrectomy may be justified. This may still be true even if there is contralateral minor reflux into an unscarred kidney with an undilated ureter, as it has recently been shown that conservative management when the ureter is undilated results in cessation of reflux in over 80% and satisfactory renal growth (Edwards *et al.*, 1977).

We conclude that there is a 12.8% incidence of hypertension developing in patients whose reflux was treated surgically on follow-up over 10 years later. Hypertension was diagnosed late (mean 12 years after surgery) and all patients therefore require close surveillance of blood pressure. However, patients whose kidneys are still unscarred 6 months after surgery are unlikely to develop hypertension.

Acknowledgements

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Addendum

Since preparing this paper for publication we have heard that 2 patients who were classified as mild hypertensives have developed further elevations of their blood pressures and will require treatment.

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The Use of Pure Carbon Stomata (Biocarbon) in Urinary Diversion

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Summary—A new synthetic material, Biocarbon, has the advantages of tissue compatibility and chemical inactivity, so that there is minimal salt sedimentation.

Experiments with animals extending over a period of more than 2 years showed good healing after various surgical and urological operations.

Biocarbon stomata were then used for vesicostomies in 6 patients. The period of follow-up has been 15 months.

We conclude that Biocarbon implants used for ureterocutaneostomies and for various conduit operations can improve the care of stoma patients.

In recent years the situation of the stoma patient has improved substantially because of the activity of stoma therapists and of ILCO (Geile and Lange, 1977). Recent technical advances include the continent ileal bladder (Leisinger *et al.*, 1974) and the Erlangen magnetic seal. At the present time the only data available to the urologist on the magnetic stoma are of an experimental nature (Wilhelms *et al.*, 1978). In addition to the usual stoma problems of hernia, retraction and prolapse, the urologist must contend with the problem of urinary incontinence with resulting smell and skin irritation. Stomal stenosis is especially troublesome with ureterocutaneostomy.

The basic requirements for a stoma device are, therefore, water-tight and gas-tight closure as well as freedom of movement for the patient. The device itself should be as inconspicuous as possible, adhere tightly to the skin and be tissue compatible.

Several experimental series using animals with stoma prostheses have been carried out in order to solve these problems (Jurkovic and Schwarzhaupt, 1972; Kelami *et al.*, 1973). Stomata of ethylene polymers or Teflon felt have been used but difficulties with alloplastic stoma materials have included urinary tract infection, encrustation and tissue incompatibility. We report on the experimental and clinical use of pure carbon stomata in urinary diversion.

Materials and Experiments on Animals

A new synthetic material—Biocarbon*—is a carbon polymer with good heat and electrical conductivity, insensitive to either high or low temperatures; it is light, hard and impermeable to both fluids and gases; it is chemically inactive and lacks galvanic activity in salt solutions, and its exceptional smoothness is important in relation to encrustation problems. Long-term experiments have demonstrated good tissue compatibility (Mooney *et al.*, 1974). In Tübingen, experiments on animals with Biocarbon implants have been performed since 1975 (Table). Various stoma forms were available for the different drainage operations (Fig. 1). In the period of observation there has been continent urine drainage, no encrustation and good healing of the implant (Harzmann *et al.*, 1978).

Table Studies on animals with 41 Biocarbon® implants (Harzmann *et al.*, 1978)

Operation	*No.*	*Observation time*
Subfascial implantation	10	14–27 months (6)
Caecostomy	9	11–22 months (6)
Ileostomy	10	11–22 months (6)
Vesicostomy	12	9–16 months (2)

Read at the 34th Annual Meeting of the British Association of Urological Surgeons in Brighton, June 1978.

*Bentley laboratories, Inc., Irvine, California, USA.

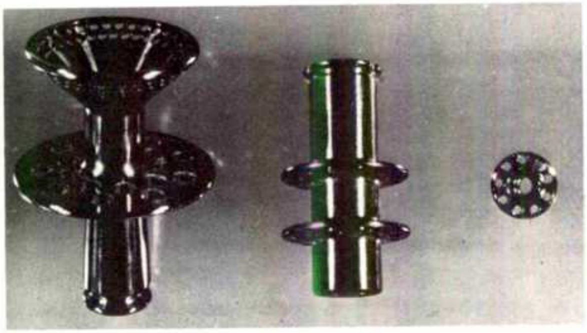

Fig. 1 Biocarbon stomata for use in animal experiments: on the left a vesicostoma; in the middle an ileostoma; on the right a stoma for ureterocutaneostomy.

Clinical Investigations

We used carbon polymer stomata for the first time 15 months ago for a vesicostomy. To insure against leakage the stoma was provided with a Dacron sleeve (Fig. 2). This operation has been performed on 6 patients who have been followed up for periods of 3 to 15 months.

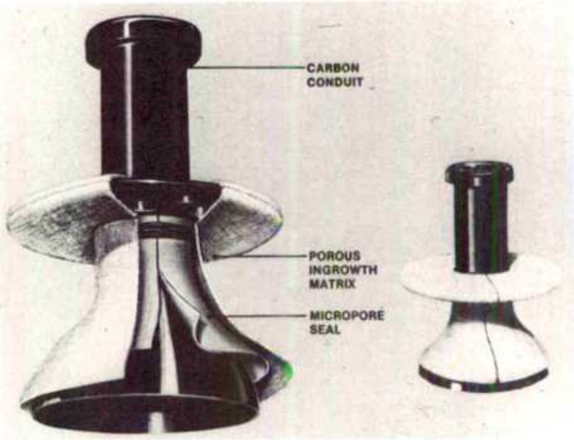

Fig. 2. Biocarbon vesicostoma with double-ply Dacron/ Velour sleeve for clinical use.

The indication for implantation was usually neurogenic bladder but was, in one case, a urethral carcinoma which had been treated with radiotherapy and which obstructed the urethra. During an observation period of 15 months there was continent drainage and stable healing without severe tissue reaction, but a slight tendency for the stoma to form encrustations. The schematic representation (Fig. 3) outlines the operation: the rectus muscle is closed under the transverse plate with the fascia on top. The Dacron sleeve serves as an infiltration zone for the surrounding muscle and fascia. In order to obtain firm fixation of the skin to the transverse plate a suture ring is fitted on at the end of the operation (Fig. 4). The drainage system is then attached over a snap-on connection (Fig. 5). Figure 6 shows the condition 10 months after a Biocarbon vesicostomy.

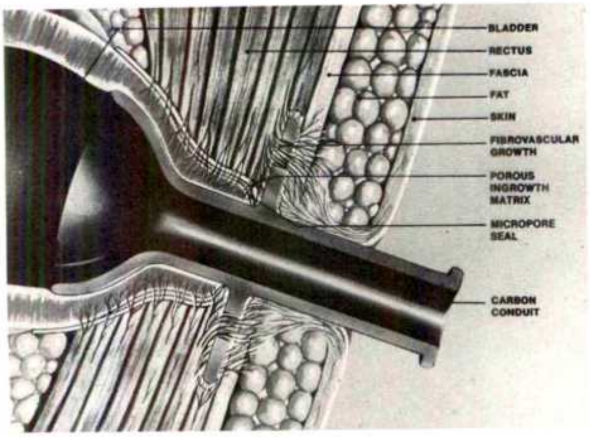

Fig. 3 Schematic representation of a Biocarbon vesicostomy.

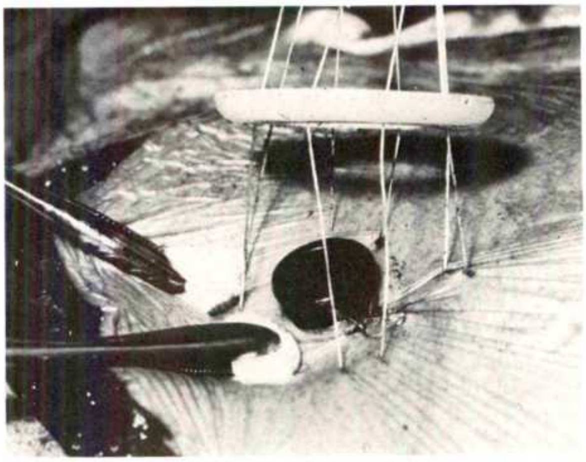

Fig. 4 Knotting on the suture ring for firm fixation of the skin to the transverse plate.

In co-operation with Dr Hauri of Zürich (Hauri, 1978), we are observing 2 patients with a continent ileal bladder in which a special Biocarbon stoma (Fig. 7) was used for urine drainage.

Conclusion

Our experience with Biocarbon stomata indicates that this substance is very suitable for urological

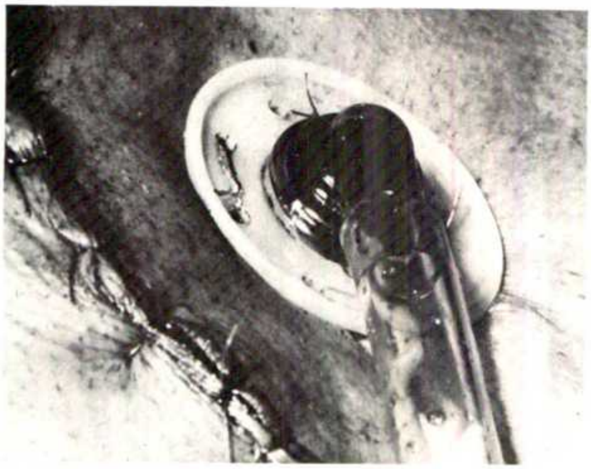

Fig. 5 View at the close of operation: drainage system has been attached to the soma by means of a snap-on connection.

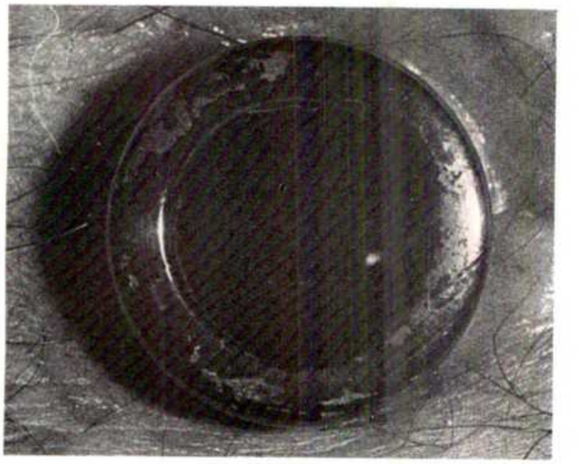

Fig. 6 Ten months after Biocarbon vesicostomy.

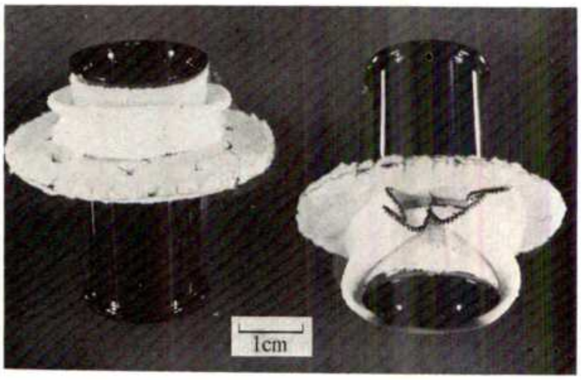

Fig. 7 Stoma for ileal conduit. Double-ply Dacron sleeve.

stomata. Its unusually good tissue compatibility as well as its very slight tendency to form salt sedimentations are points to emphasise. Clinical observations of 6 vesicostomies support its use in ureterocutaneostomy and in ileal and colonic conduits. This new carbon polymer will probably be most frequently used in ureterocutaneostomy. Relevant experiments on animals are now in progress, together with associated experimental and clinical testing of the applicability of this alloplastic stoma to ileal and colonic conduits.

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Total Cystectomy—A Review

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Summary—Analysis of 99 total cystectomies for malignant disease over a 10-year period in one unit has been carried out, in order to clarify the place of the operation in the overall management of the disease and to assess the quality of life in the patients so treated.

Cystectomy is one of the more exacting and time consuming operations in urology. It takes up the best part of an operating list which might have been devoted to 3 or 4 prostatectomies or 10 or more lesser procedures. It is associated with a certain mortality and morbidity, and may result in a bed being occupied by a single patient for a substantial period. Apart from these practical considerations the operation is a mutilating one and the urinary diversion, whichever method is chosen, is a sorry substitute for a healthy bladder. Furthermore, a high proportion of patients who have a cystectomy for cancer will not be cured by the procedure. The proposition "alternative methods of treatment for cancer of the bladder have now progressed so far that cystectomy for cancer will no longer be necessary" is surely one that would be welcome to all urologists. That day has not yet arrived so that the acquisition of skill in the technique of cystectomy and of experience in the management of the problems with which it is associated must remain an essential part of the training of a urologist.

Our policy in individual patients has been determined very largely on an *ad hoc* basis. We have reviewed our indications for operation and the results obtained, both in the quality of life for the patient and in the management of his disease. Cystectomy for benign conditions has been excluded.

Patients and Methods

Ninety-nine cystectomies for malignant disease carried out in our department in the 10-year period 1966 to 1977 were reviewed. There were 68 males and 31 females, with ages between 38 and 80 years (mean 65.5 years). Ninety had transitional cell carcinomas, there were 2 sarcomas, and the remainder were done for tumours of the urachus (1 case), cervix (2 cases), vagina (2 cases) or prostate (1 case). One tumour was probably a secondary tumour of the bladder. Table 1 divides the larger group according to the UICC classification. The indications for operation are shown in Table 2. The series includes a group of T3 cases treated by elective cystectomy after 4000 rads as advocated by Whitmore (1969) and Wallace and Bloom (1976). We treat some 100 new cases of bladder cancer each year, so approximately 9% of those come to cystectomy.

Our policy has been to carry out, wherever possible, a total cystectomy with stripping of the pelvic wall below the bifurcation of the iliac arteries. The uterus and the anterior vaginal wall were removed in females, while in the male the prostate and seminal vesicles were always taken. Urethrectomy was included in 20 patients with multi-focal growths, as a combined procedure, and a subsequent urethrectomy was necessary in 4 cases. Urinary diversion was done by an ileal conduit with the "69" uretero-ileal anastomosis (Wallace, 1970), though ureterocolic anastomosis was carried out in 16 cases in this series. All patients with stomas attended a special Loop

Table 1 TNM Classification and Number of Survivors in 90 Patients with Transitional Cell Carcinoma

	Alive	*Total*
T1S	2	2
T1	10	17
T2	10	24
T3	14	41
T4	3	6
Total	39	90

Read at the 34th Annual Meeting of the British Association of Urological Surgeons in Brighton, June 1978.

Table 2 Indications for Cystectomy in 90 Patients with Transitional Cell Carcinomas

Immediate policy	15
Elective after 4000 rads	20
Salvage	41
Palliative	10
Emergency (haemorrhage)	4
Total	90

Out-patient Clinic and enjoyed the help of an appliance fitter.

Results

The operative mortality is shown in Table 3. Five patients died as the direct result of the operation, although 2 of these had left hospital only to return with pelvic complications. Operative mortality, therefore, was approximately 5%.

Complications are shown in Table 4. Post-operative urine leakage has been not uncommon in our patients, particularly in those cases in which the ureteric anastomosis has not been splinted, but with one exception this has never caused us any significant concern and the leak dried up spontaneously without surgical intervention. There have been a number of stoma problems but these have been amenable to surgical correction. Six of 16 patients had complications after ureterocolic diversion and 2 were converted to ileal loops.

Seventy-two patients were previously treated by endoscopic diathermy/resection (26 cases) or radiotherapy (24 cases) or both (22 cases), and 10 patients had had open operations carried out in other hospitals. These treatments were carried out over periods ranging from a few months to 28 years previously (Table 5) and do not appear to have altered significantly the results of salvage cystectomy.

Table 3 Operative Mortality and Causes of Death (all cases)

Cause of death	*Time after operation*	*Number of cases*
Reactionary haemorrhage —renal failure	5 days	1
Acute obstruction —burst abdomen	1 week	1
Pelvic abscess —acute obstruction	6 weeks	1
Late faecal fistula —secondaries	6 weeks	1
Steroids for D.L.E. —failure to heal	3 weeks	1
Total		5 (5.05%)

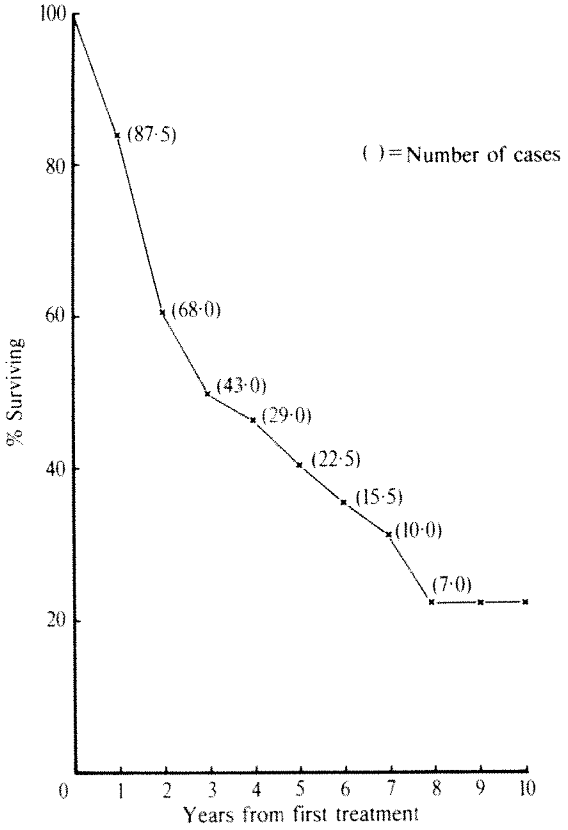

Fig. 1 Life-table survival rate.

Table 4 Complications (All Cases)

Minor	
Wound abscess 4	Incisional hernia 4
Urine leak 5 (5-18 days) all stopped spontaneously	
Major	
Non-operative	*Operative*
Cardiac arrest 2 (1 died)	Reactionary haemorrhage 2 (1 died)
Pulmonary embolus 3	
Renal failure 4 (1 died)	
Faecal fistula 2	Faecal fistula 2 (1 died) Acute obstruction 6 (2 died) Urine leak 1 Anuria 1
Stoma 5—2 retraction, 1 hernia, 1 prolapse (×2), 1 ulceration	
Ureterocolic 16	
Alive 5	(complications: 1 acidosis, 1 staghorn)
Dead 11	(complications: 4 acidosis) (2 converted to ileal loop).

Table 5 Effects of Delay on the Outcome of Cystectomy (90 Patients with Transitional Cell Carcinomas)

State	*Duration of delay*			
	Minimum	*Maximum*	*Average*	*Number*
Alive	6 months	28 years	4.8 years	31/39
Dead	14 months	15 years	7.4 years	33/40

This series, concluded in December 1977, does not permit valid survival figures to be calculated. However, a Life Table analysis (Fig. 1) reveals 3 and 5 year survival of those at risk of 51% and 41% respectively. Analysis of these results by clinical staging (Fig. 2) showed a survival in T1 and T2 cases of 63% and 41% respectively, whereas the 34% of T3 cases still living include several recently treated patients, and at least 2 alive with disease.

The results in patients treated by radiotherapy are shown in Table 6. In our series the survival rate after pre-operative radiotherapy (4000 rads in 4 weeks) followed by elective cystectomy has been extremely poor, and 85% of the patients have died. By contrast, there was a 48% survival rate in selected patients treated by salvage cystectomy when radical radiotherapy (6000 rads in 6 weeks) had failed to eradicate the disease. This group of patients includes 8 T2 growths, which must favour the results, but this is in part offset by 3 T4 cases. For comparison we have included 30 cases of T3 disease treated by radical radiotherapy alone, and 79% have died.

The quality of life sustained by the post-cystectomy patient was assessed in terms of the period of symptom-free life in those who subsequently died of their disease, *i.e.* not including the terminal stages of the illness. There was an average

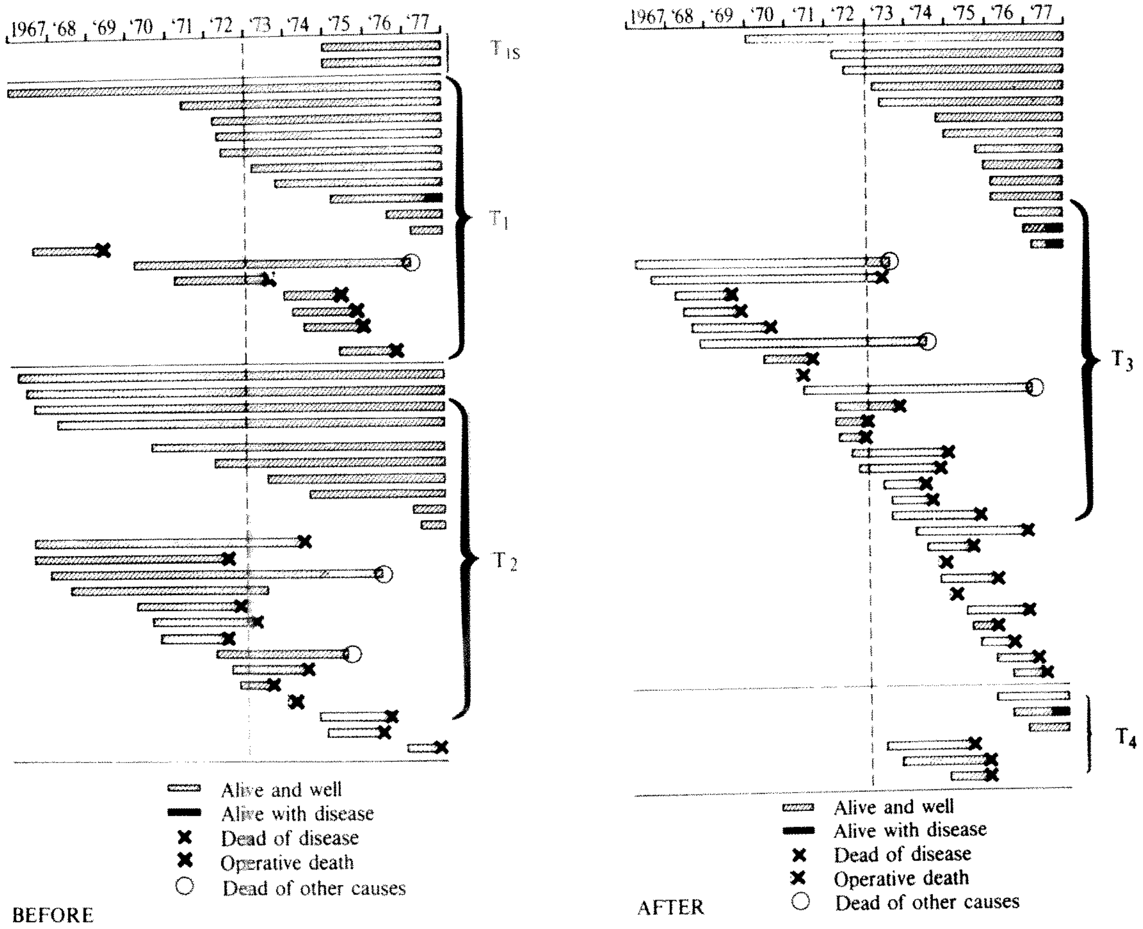

Fig. 2 Survival related to TNM classification and time before and after cystectomy.

Table 6 Number of Survivors Related to Dose of Radiotherapy and Cystectomy Policy in 90 Patients with Transitional Cell Carcinomas Compared to Survival Rate after Radical Radiotherapy alone without Cystectomy

Radiotherapy dose	*Type of cystectomy*	*Number of cases*	
		Alive	*Total*
4000 rads	Elective	3 (15%)	20
6000 rads	Salvage	12 (48%)	25
3150 rads (incomplete)	Salvage	0	1
6000 rads	None	7 (23%)	30

survival without symptoms of 16 months in the 55 patients who ultimately died. Forty-four patients are still alive following operation for periods up to 11 years, with average survival of 4.5 years.

An unexplained observation was the sex difference in the survival figures. Sixty-six per cent of the male patients have died, compared with 35% of women. This is not related to the staging of the disease, which was markedly less favourable in women (80% of women had T3 or T4 lesions compared with 60% of the men).

Discussion

It would be naive to expect exceptionally good results in the management of carcinoma of the bladder from the conventional policy that has been adopted, and the apparently favourable results must be interpreted with caution in terms of small numbers and varied length of follow-up. However, the failure of pre-operative radiotherapy with elective cystectomy to improve our results is striking, and in marked contrast to the findings of Whitmore (1969), Werf-Messing (1973) and Wallace and Bloom (1976).

By contrast, salvage cystectomy, often carried out after many years of conservative treatment, has proved unexpectedly satisfactory and has not been attended by a high mortality of 20% reported by Wallace (1973). We have not found that early salvage operations are less complicated than when fibrosis is established, as suggested by Wallace and Bloom (1976), and our operative mortality of 5%, while not approaching the 2.3% reported by Deweerd and Colby (1973), is acceptable, particularly in the light of the high percentage of salvage operations. We seek of course to improve our results and hope that adjuvant chemotherapy may have something to offer.

Of equal importance in this review was the quality of life of these patients. They were freed from their miserable bladder symptoms and their endless check cystoscopies, and a period of up to 4 years of symptom-free life, even in the ultimately fatal cases, appears to be good palliation. Cystectomy therefore would seem to remain an operation of considerable benefit and we would now advocate its use when it appears at the outset to be the only available treatment, and as a salvage procedure when other methods have failed. In particular, the operation can provide great relief to patients whose bladder symptoms have become intolerable.

Acknowledgements

We wish to record our gratitude to Dr R. G. Skeet of the South Thames Cancer Registry for assistance with the Life Tables, and to Miss Beryl Walbridge, our secretary, for her invaluable assistance with the typescript.

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Radical Cystectomy for Carcinoma of the Bladder

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Summary—A personal series of 50 radical cystectomies has been reviewed to decide whether it is a justifiable operation and, if so, when it should be performed.

In spite of the fact that radical cystectomy had a higher operative mortality than simple cystectomy and was sometimes followed by lymphoedema, in patients with invaded iliac lymph nodes it was followed by a 25% 5-year survival. It appears, therefore, to be a justifiable procedure.

It is recommended that simple cystectomy should be performed for patients with papillomatosis, carcinoma *in situ*, and as a salvage procedure after radiotherapy has failed, and that radical cystectomy should be reserved for elective cases of invasive vesical tumours, and for those patients who are found at exploration to have obvious metastatic deposits in the iliac lymph nodes.

In radical cystectomy the iliac lymph nodes are removed with the bladder. Daughtry *et al.* (1977) have compared the results of simple and radical cystectomy over a 10-year period at the Cleveland Clinic. They reached the provocative conclusion that radical cystectomy has little justification, firstly because it has a higher operative mortality than simple cystectomy, and secondly because none of their patients with invaded lymph nodes survived 2 years.

This study presents the results of 58 cystectomy patients with a possible 5-year survival and it seeks to answer 2 questions: is radical cystectomy justifiable and, if so, in which cases?

Patients and Methods

From February 1967 until April 1973, 58 patients have had cystectomy performed for carcinoma of the bladder. Fifty had radical and 8 simple cystectomy. The number of simple cystectomies is too small to analyse in detail. Of the radical cystectomies, 38 were men and 12 women. Eight were aged between 35 and 55, 31 between 55 and 70 and 11 were over 70 years. Half of the patients had elective and half salvage cystectomy, radiotherapy having failed. The indications are shown in Table 1: elective cystectomy was usually performed for invasive tumour, occasionally for papillomatosis which was beyond endoscopic control; the commonest indication for salvage cystectomy was persistent bleeding and all of the patients had either residual or recurrent tumours, often multiple and extensive.

Pre-operative radiotherapy was given to 7 of the 25 elective radical cystectomy patients. Some were treated with a dose of about 4000 rads in 3 weeks, followed by cystectomy within 4 weeks; others with 2400 rads in 1 week, followed by immediate cystectomy.

Cystectomy and urinary diversion were always a one-stage procedure. Five of the earlier cases had a ureterocolic anastomosis and 1 a rectal bladder; the rest had an ileal conduit and this is now the routine method of urinary diversion; the ureters were joined to the ileum end-to-end using the "Y" anastomosis (Clark, 1978). In men, both for simple and radical cystectomy, the seminal

Table 1 Indications for Radical Cystectomy

Elective		*Salvage*	
Papillomatosis	6	Residual tumour	15
Invasive tumour	14	Recurrent tumour	10
Ureteric obstruction	5		
Total	25		25
		(with persistent bleeding	16)

Read at the 34th Annual Meeting of the British Association of Urological Surgeons in Brighton, June 1978.

Table 2 Operative Mortality After Radical Cystectomy

	Elective	*Salvage*
Pulmonary oedema	1	1
Wound infection and sepsis	1	1
Pulmonary embolus		1
Ileus and uraemia		1
Inhaled vomit		1
Total	2	5

vesicles and prostate were removed with the bladder; in women, anterior exenteration was performed.

For radical cystectomy, the fat and fascia around the bladder and the lymph node chains from the bifurcation of the common iliac artery to the inguinal ligaments were removed *en bloc* with the bladder, ligating the arteries at their origin from the internal iliac. The lymph nodes around the common iliac artery were also removed when they were enlarged.

The whole length of the urethra was removed in only 3 of the 38 men. Two patients had 1 kidney and its ureter removed *en bloc* with the bladder and urethra.

The operation was almost always performed under epidural or spinal anaesthesia to reduce bleeding, and through a wide transverse lower abdominal incision. A light general anaesthetic was also given to keep the patient asleep through the operation, which usually lasted from 3 to 5 h.

Results

There was no operative mortality from simple cystectomy; that from radical cystectomy was 14%. The causes of death are listed in Table 2. Sudden pulmonary oedema killed 2 patients on the second post-operative day and has led to the routine monitoring of central venous pressure. Of the 7 patients who died 5 had had salvage cystectomy, making the operative mortality for elective radical cystectomy 8% and that for salvage radical cystectomy 20%.

Table 3 Late Complications After Radical Cystectomy

Ileal conduit		*Other*	
Stomal stenosis	5	Urethral carcinoma	1
Ureteroileal stenosis	1	Ureteric carcinoma	3
Hernia alongside stoma	1	Intestinal obstruction	2
Ureterocolic anastomosis		Ileovaginal fistula	1
Hyperchloraemic acidosis	1	Oedema	10

Leakage from the ureteroileal anastomosis (1 patient) was treated by bilateral nephrostomy, from the intestinal anastomosis (1 patient) by resuture. One patient developed osteitis pubis. Late complications (Table 3) are divided into those associated with the urinary diversion and other complications.

There was a significant incidence of oedema (Table 4). Sometimes the oedema was pitting oedema and transient; sometimes it was non-pitting, permanent and distressing to the patient. Permanent lymphoedema sometimes occurred years after cystectomy and preceded death from carcinomatosis by only a few months; sometimes it persisted for years and, as there was no evidence of recurrent tumour, was presumably caused by damage to lymphatic channels.

The cause of death within 5 years in 25 patients was usually carcinomatosis (15 patients); some died from other tumours (2 with ureteric unrelated tumour) and other unrelated causes (2). Two cases have been lost to follow-up, are presumed dead and the cause of death in 3 is unknown. No patient died from renal failure.

Five-year survival is shown in Table 5. After simple cystectomy it was 50%; after radical cystectomy 36%. After elective radical cystectomy it was 28%; after salvage radical cystectomy 44%. These differences can be explained to some extent by the different operative mortality and proportion of Stage T1 or A cases in the 4 groups. When post-operative deaths have been excluded the difference between the 5-year survival after simple and radical cystectomy becomes less—50 and 42% respectively—whereas that between elective and salvage radical cystectomy becomes greater—30 and 55% respectively. These corrected 5-year survivals are mirrored to some extent by the percentage of Stage T1 or A cases in the 4 groups.

The 5-year survival after radical cystectomy according to the stage of the tumour, both by the TNM and the Jewett classifications, is shown in Table 6. These are uncorrected figures. It is of note that 3 of the 12 patients with lymph node

Table 4 Oedema After Radical Cystectomy

Pitting 4/43	(9%)	*Non-Pitting* 6/43	(14%)
Transient	2	Died within 1 year	4
		Survived 6-7 years	2

Table 5 5-Year Survival After Cystectomy

	Number of cases	*5-year survival*	*Operative mortality*	*Corr. 5-year survival*	*Proportion Stage T1/A*
Simple cystectomy	8	50%	0%	50%	50%
Radical cystectomy	50	36%	14%	42%	46%
Elective rad. cystectomy	25	28%	8%	30%	24%
Salvage rad. cystectomy	25	44%	20%	55%	72%

metastases (Stage D_1) survived 5 years. Elective radical cystectomy had been performed in all 3 cases and none had received radiotherapy. One had 5 glands involved and another the highest gland in the chain. One remains well 10 years after cystectomy. The cases of lymph node metastasis are analysed further in Table 7.

The accuracy of diagnosing lymph node metastasis at the time of operation is assessed in Table 8. Two patients with apparently normal nodes had metastases on histology; both had elective cystectomy for invasive tumours. Fourteen patients with enlarged nodes had no metastases on histology, and the enlargement was presumably an inflammatory response.

The 5-year survival for the 7 cases of elective radical cystectomy who received pre-operative radiotherapy was almost identical to that in the 18 cases who received none—29 and 28% respectively.

Discussion

There seems little doubt that the operative mortality for radical cystectomy is greater than that for simple cystectomy. Although Whitmore and Marshall (1962) recorded an identical operative mortality of 14% for both simple and radical cystectomy, Cordonnier (1968) recorded one of 4.6% for simple cystectomy. The mortality of the Cleveland Clinic (Daughtry *et al.*, 1977) was 16% for radical and none for simple cystectomy—very similar to that for this series (14 and 0%). Realistic mortality figures would probably be 5% for simple and 10% for radical cystectomy, and 10% is in fact my own operative mortality for radical cystectomy in the last 5 years.

What are the chances of a patient with lymph node metastasis surviving for 5 years after radical cystectomy? Marshall and Whitmore (1956) decided that if more than 2 lymph nodes were invaded radical surgery was contraindicated; in 1962 they recorded a 4% 5-year survival. Dretler *et al.* (1973) excised the whole of the iliac lymph node chains, as in Wertheim's hysterectomy, and later recorded a 33% 5-year survival for those with only 1 or 2 nodes involved, and a 17% 5-year survival for all cases. Daughtry *et al.* (1977) had no long-term survivors; in this series a 25% 5-year survival is recorded for all cases.

Ideally, radical cystectomy should be performed only for those cases with invaded lymph nodes. The difficulty is in diagnosis. Lymphography is of limited value with early invasion, and this series has shown the difficulty in deciding at operation which nodes are invaded; even nodes which appear normal may contain tumour.

Radical cystectomy has several disadvantages. It has a higher operative mortality than simple cystectomy; it may be followed by lymphoedema; it is more difficult to perform and takes longer. The only reason for performing it, rather than simple cystectomy, is to cure patients with invaded lymph nodes, and the chances of doing this must be weighed against its disadvantages, especially against its higher operative mortality.

It is recommended, therefore, that simple cystectomy should be performed routinely for patients with papillomatosis, carcinoma *in situ* and as a salvage procedure—these patients had a relatively low incidence of lymph node metastasis in this series—whereas radical cystectomy should be reserved for elective cases of invasive tumours of the bladder—which had a high incidence—and for those patients who are found at exploration

Table 6 Radical Cystectomy: 5-Year Survival and Stage

T1 = A	*T2 = B_1*	*T3*	*T4*	*Unknown*	*Total*	*B_2*	*C*	*D_1*
$\frac{12}{23} = 52\%$	$\frac{0}{3} = 0\%$	$\frac{4}{19} = 21\%$	$\frac{1}{3} = 33\%$	$\frac{1}{2} = 50\%$	$\frac{18}{50} = 36\%$	$\frac{2}{6} = 33\%$	$\frac{0}{4} = 0\%$	$\frac{3}{12} = 25\%$

Table 7 Radical Cystectomy: Incidence of Lymph Node Metastasis

	Elective	*Salvage*
Invasive tumours	42%	13%
Papillomatosis	17%	10%

to have obvious metastatic deposits in the iliac nodes.

Salvage cystectomy in this series had a high operative mortality. Many of the patients had been bleeding for months and were poor operative risks. However, the high 5-year survival showed that the procedure was fully justified. Often, when radiotherapy has been given a long time before, it was easier to remove the bladder by dissecting it out near the pelvic wall; it is recommended that lymphadenectomy should be performed only when the nodes are obviously invaded.

Table 8 Accuracy of Operative Assessment of Lymph Nodes in 41 patients

	Histology of lymph nodes	
Operative findings	*Normal*	*Invaded*
Nodes normal	16	2
Nodes enlarged	14	9

In this series, as in the Cleveland Clinic series, no benefit was found from pre-operative radiotherapy, and the value of this before cystectomy remains *sub judice*.

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Longitudinal Study of Bladder Cancer with Cytology and Biopsy

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Summary—A study of urinary cytology and selected mucosal biopsies in conjunction with cystoscopy provided additional information of value in the management of 318 patients with bladder cancer. These procedures were especially helpful in patients with no visible lesion on follow-up cystoscopies in assessing the bladder epithelium, the behaviour of which may be unpredictable in that no further tumours may occur, or they may arise at irregular intervals.

The study of urinary cytology and selected bladder mucosal biopsies provides additional material of value in classifying patients for further treatment and may have considerable prognostic significance. This report presents results from a prospective clinical investigation in which 318 bladder tumour patients were evaluated over a 4-year period. Most of these patients had had cystoscopies, cytology and tumour biopsies as part of the initial evaluation or follow-up examinations. During the period of observation, 1265 specimens of bladder washings and urinary cytology and 758 tumour and/or selected mucosal biopsies were obtained. Since the prognosis may depend primarily on the nature and extent of changes in urothelium remaining after the removal of visible lesions, the value of longitudinal studies of urinary cytology and selected mucosal biopsies in detecting field changes in patients with bladder cancer is assessed.

Materials and Methods

Between January 1974 and March 1978, 318 patients with bladder tumours were seen and treated at the University of Iowa. The initial evaluation and follow-up of these patients resulted in 1090 cystoscopic examinations. Specimens of 1265 bladder washings and urine cytology were collected. Tumour and/or selected mucosal biopsies were performed in 758 instances. Stage, grade, location and gross appearance of the lesions were recorded.

Each time a patient had cystoscopically visible tumour, a deep biopsy of the neoplasm was obtained by electroresection for study of histological characteristics. Mucosal biopsy specimens were also obtained by cold punch technique from pre-selected normal-appearing sites (one lateral to each ureteric orifice, and one on the mid-posterior bladder wall) and areas adjacent to the tumour. When no tumour was visible but the cytology of the urinary bladder washings or urine was positive, biopsy specimens were obtained from the pre-selected normal-appearing sites and any areas which appeared suspicious. The site of each visible lesion and the site of each mucosal biopsy was recorded on a diagram or "map of the bladder" (Fig.). The presence of recurrent tumour, if any, the interval between the initial tumour diagnosis and resection and the site of recurrent tumour were recorded. All specimens were examined grossly and then processed, embedded in paraffin, sectioned and stained with Haematoxylin and Eosin.

Bladder urine and saline bladder washings were obtained during cystoscopy from patients with suspected bladder tumour as well as from patients who were under surveillance. Bladder urine was collected through a urethral catheter. The bladder wash consisted of 50 ml of saline alternately injected into and aspirated from the bladder 5 times. The catheterised urine sample and saline bladder washings were collected separately in sterile containers. The volume and appearance were immediately recorded. An equal part of 50% ethyl alcohol was added and the container gently agitated and refrigerated until ready for preparation. All or part of each specimen was

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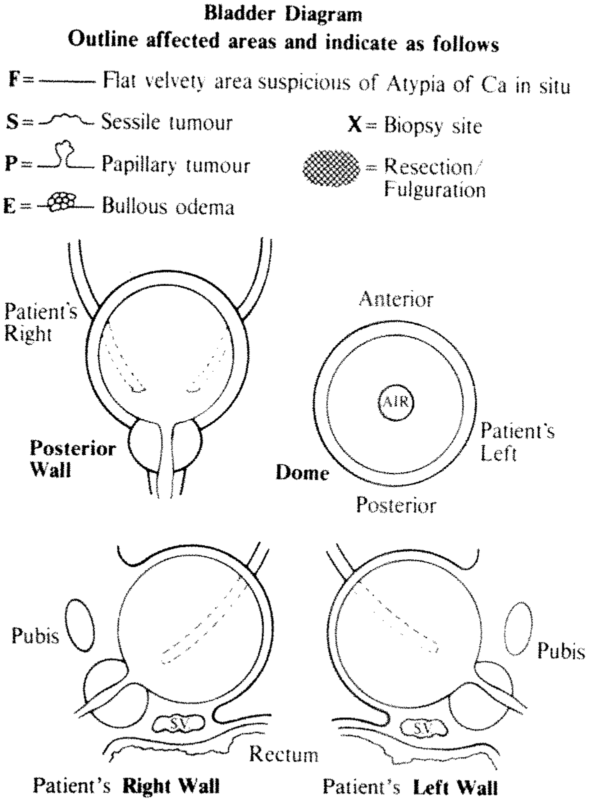

Fig.

passed through 2 or more 8 micron Millipore filters. They were fixed overnight in 95% ethyl alcohol and stained with a modified Papanicolaou staining technique.

One of 6 diagnostic categories was used to describe each cytology slide: (a) negative, (b) atypical cells present compatible with inflammatory origin, (c) radiation changes or drug effects, (d) suspicious for transitional cell cancer, (e) strongly suggestive for transitional cell cancer and (f) tumour cells definitely present. We are currently investigating our cytology specimens for changes typical of cancer *in situ*. Only the patients in whom tumour cells could definitely be identified were reviewed in this report.

Results

Of 318 patients with a documented history of bladder tumour, 299 patients (94%) had cystoscopy as part of their initial evaluation. The morphological descriptions of the tumours found during initial cystoscopy are listed in Table 1. At the time of our first evaluation, tumour was visible on cystoscopy in 278 patients, with some patients showing more than one tumour type. No tumour was visible in 18 patients who had undergone treatment before coming to our institution. Two patients had no visible tumour but were evaluated because of recurrent cystitis with bladder biopsy revealing carcinoma *in situ*. Cystoscopy was positive, but no morphological description of tumour was recorded in 9 patients. Follow-up cystoscopic examinations showed no significant difference in tumour distribution from that found at the initial cystoscopy (Table 2).

A total of 661 descriptions of tumour sites was recorded. The locations of these lesions are listed in Table 3. Follow-up cystoscopic examinations were positive in 271 of 791 examinations. Except for fewer tumours in the area of the trigone and lateral bladder walls, no appreciable difference in the distribution of tumours compared to the initial evaluation was found. Cystoscopy was considered positive not only when gross tumour was identified, but also when a suspicious area was seen which was histologically proven to be neoplasm. In 314 examinations cystoscopy, cytology and bladder biopsies were performed. A correlation of our cystoscopic findings with cytology and biopsy results is listed in Table 4.

When the results of the initial and follow-up examinations are combined, tumour and/or selected mucosal biopsy confirmed the positive cystoscopic findings in 230 examinations (93%). In 18 (17%), suspicious areas were biopsied during cystoscopy, but the pathology findings were

Table 1 Morphology of Tumours

Tumour type	*No.*	*Patients with visible tumour (%)*
Papillary	179	64.4
Flat	29	10.4
Sessile	102	36.7
No visible tumour	20	
Suspicious area	1	
No tumour description	9	

* Some patients had more than one tumour type.

Table 2 Type of Tumour at Follow-up Cystoscopies

Tumour type	*No.*	*Follow-up exams with visible tumours (%)*
Papillary	153	56.5
Flat	46	17.0
Sessile	81	29.9

Table 3

Site of primary tumour			*Site of tumour on follow-up*	
Tumour site	*No.*	*Patients with visible tumour (%)*	*No.*	*Follow-up exams with visible tumours (%)*
Trigone	87	31.3	51	18.8
Neck	91	32.7	76	28.0
Left wall	84	30.2	55	20.3
Right wall	96	34.5	65	24.0
Right orifice	61	21.9	41	15.1
Left orifice	66	23.7	39	14.4
Posterior wall	52	18.3	56	20.7
Anterior wall	35	12.6	20	7.4
Dome	46	16.5	51	18.8
Prostatic urethra	26	9.3	21	7.7
Prostate	12	4.3	3	1.1
Other	5	1.8	3	1.1
	661		481	

negative. In 32 examinations (48%), the selected mucosal biopsies were positive although on gross inspection of the bladder no abnormalities were noted. In 34 examinations (52%) both the cystoscopic findings as well as the selected mucosal biopsies were negative.

The cytology and biopsy findings were both positive for tumour in 178 (71%) of the 248 examinations with positive cystoscopy, while in 28 (42%) of the 66 examinations with negative cystoscopy, both these tests were negative. Cytology and biopsy were negative in 7 examinations (3%), although cystoscopy revealed a suspicious area. In contrast, 24 (36%) of those examinations with negative cystoscopy had positive cytology and biopsy. In 52 examinations (21%) the cytology was negative and did not confirm the positive cystoscopic and pathological findings. Positive cytology was found in 6 examinations (9%), although the selected mucosal biopsy and cystoscopy were both negative. In 11 examinations (4%), a positive cystoscopy and cytology could not be confirmed by bladder biopsy. This contrasts with 8 examinations (12%) in which the selected mucosal biopsies were positive although cystoscopy and cytology were both negative.

Table 4 Correlation Between Findings on Cystoscopy, Cytology and Biopsy at Initial and Follow-up Evaluations

	A. Cystoscopy: positive			
		Cytology		
		Positive	*Negative*	
Biopsy	Positive	178	52	230
	Negative	11	7	18
		189	59	248

	B. Cystoscopy: negative			
		Cytology		
		Positive	*Negative*	
Biopsy	Positive	24	8	32
	Negative	6	28	34
		30	36	66

A further correlation between the various biopsy findings and cytology reports is provided in Table 5. Of 110 examinations with negative cytology specimens, 55 (50%) showed either transitional cell cancer or carcinoma *in situ* in the biopsy specimens, while 20 (18%) showed atypia and 35 (32%) corresponded with the negative cytology results. In 218 cytology specimens, transitional cell cancer was either identified or suspected, and the biopsy confirmed these findings in 186 specimens (85%), most of which (53%) showed transitional cell cancer, grade III. In 32 patients (15%), the biopsy readings were either negative or showed only atypia while the cytologies were suggestive for transitional cell cancer.

The initial tumour grade and stage did not affect the 12-month recurrence rate as shown in Tables 6 and 7. The 12-month overall recurrence rate was 47.1% (65/138).

Table 5 Correlation Between Cytology and Biopsy Findings at Initial and Follow-up Evaluations

Cytology	*Biopsy*												*Total*	
	Atypia		*Negative or normal*		*TCC grade I*		*TCC grade II*		*TCC grade III*		*CIS*			
Negative or normal		20		35		17		19		15		4		110
Inflam changes		1		4		0		0		6		0		11
Rad/drug effect		6		5		0		1		2		1		15
TCC	15	8	17	8	12	4	56	35	98	85	20	16	218	156
Suspicious for TCC		5		8		8		18		11		2		52
Strongly suggestive of TCC		2		1		0		3		2		2		10
CIS		0		0		0		0		0		1		1
														355

Discussion

From clinical experience it is known that the urothelium of certain patients has a tendency to develop recurrent bladder tumours. The mapping and histological studies of Koss *et al.* (1977), Farrow *et al.* (1976), Melicow (1952) and others and the giant section studies of Friedell (Soto *et al.*, 1977) and of Schade (1972) confirmed that in many cases of bladder cancer there is an associated "field change". The concept of a multicentric origin of bladder tumours was attributed to Hansemann (1890).

The distribution of bladder tumours was reported in several studies (Eisenberg *et al.*, 1960; Koss *et al.*, 1974; Koss *et al.*, 1977; National Bladder Cancer Collaborative Group A, 1977a). The lateral and posterior walls, as well as the epithelium in the vicinity of bladder tumours, are most frequently involved by pre-cancerous lesions. Others have found that the most common site for vesical tumours, primary or recurrent, is posterolateral to the ureteric orifices (Greene *et al.*, 1973). These findings have led us to biopsy routinely the area next to the tumour as well as to obtain mucosal biopsies lateral to each ureteric orifice and one in the midposterior wall. In our review, this is borne out by the fact that most tumours initially and also on subsequent visits can be found close to the trigone and the lateral bladder walls (Table 3).

The first study of exfoliated cells from bladder cancer seems to be that published by Sanders (1865). Extensive cytological studies on urine were first published by Papanicolaou and Marshall (1945). In the study by the National Bladder Cancer Collaborative Group A (1977b), tumour grades were compared with cytology findings. While in patients with grade I or II lesions the cytology confirmed the biopsy results in only 43 (47%), an excellent correlation (93%) was found in grade III lesions.

In our study in 355 examinations, cytology and biopsies were available for comparison (Table 5). In 218 patients the cytology showed malignant cells, but the biopsy was negative in 32 cases. This "false-positive" cytology rate of 14.7% can be attributed to the widely distributed microscopic mucosal alterations which appear normal on cystoscopic examination and can therefore be missed by biopsy, but form a basis for the frequently observed tumour recurrences (Kern *et al.*, 1968; Schade, 1972; Cooper *et al.*, 1977; Heney *et al.*, 1977). Of greater concern is the fact that in 136 cases in which the cytology showed no malignant cells, the biopsy was positive in 65, for a false-negative rate of 47.8%. In grade I lesions, cytology confirmed the biopsy in 41%, in grade II

Table 6 Incidence of Recurrence Compared to Tumour Grade

Initial grade	*Recurrence*		
	No	*Yes*	
I	8	8	16
II	26	26	52
III	34	25	59
	68	59	127

Table 7 Incidence of Recurrence Compared to Tumour Stage

Initial stage	*Recurrence*		
	No	*Yes*	
O or A	37	35	72
B, C, or D	30	21	51
	67	56	123

74%, in grade III lesions in 81%, and in cancer *in situ* in 80%. The trend is obvious that cytology correlated best with the higher grades of bladder cancer (Kern *et al.*, 1968; Esposti *et al.*, 1970).

Since the tendency to recurrent tumour formation is well recognised, the standard follow-up of patients with bladder tumours is to perform cystoscopy with biopsy of suspicious lesions. In 314 patients, bladder biopsies and cytologies were obtained and cystoscopies were performed (Table 4). In 8 patients (12%) only the bladder biopsy and in 6 patients (9%) only the cytology was positive when cystoscopy was negative. This demonstrates that in all patients with recurrent bladder tumours, widespread disease of the bladder may exist which cannot be fully estimated by cystoscopic examination alone. The diagnostic accuracy of urinary cytology has been reported to be between 26% and 100% with a false-positive report rate of 1 to 12% (Kern *et al.*, 1968; Harris *et al.*, 1971). Urinary cytology has not received widespread acceptance by urologists, probably because it is associated with a high incidence of false-positive as well as false-negative results. Nevertheless, it is particularly helpful in the detection of *in situ* and early invasive non-papillary cancer of the bladder, since cystoscopy in these patients may be normal or indistinguishable from changes of inflammation or other benign conditions. It is clear that none of the tests, bladder biopsy, cytology, or cystoscopy, are sufficient alone in the work-up of patients with suspicion of bladder cancer.

The practising urologist needs information to help him to determine which tumours will recur and how often to follow a patient with cystoscopy. In our study, the overall 12-month recurrence rate was 47.1% (Tables 6 and 7), and no prediction could be based on either tumour grade or stage. Over a one-year period, recurrent bladder carcinoma was noted in 33% of patients with stage O or A lesions in the surveillance study by the National Bladder Cancer Collaborative Group A (1977a). Other studies have recorded tumour recurrence in two-thirds with progression in one-third of patients who initially had low stage tumours (Kaplan *et al.*, 1951; Pyrah *et al.*, 1964; Greene *et al.*, 1973; Varkarakis *et al.*, 1974).

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The Induction of Cystitis and the Implantation of Tumours in Rat and Rabbit Bladders

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Summary—A method of inducing tumour growth in rat and rabbit bladders is described. Tumour induction is dependent on a pre-induced cystitis. In rats, tumour also grows in the kidneys because of species characteristic vesicoureteric reflux. The possible significance is discussed in relation to the management of human bladder tumours.

The origin of this study lies in the Epodyl Clinic held at St Peter's Hospital, where one of us (L.E.) assisted for 18 months. During the course of the clinical study it became apparent that Epodyl (Ethoglucid; ICI) was often a satisfactory agent for the control of multiple superficial papillary transitional cell bladder tumours as previously reported by Abbassian and Wallace (1966) and Riddle and Wallace (1971). It produces fewer systemic side effects than other agents, such as Thiotepa (triethylene thiphosphoramide; Lederle), because its higher molecular weight makes absorption less likely (Mitchell, 1971).

While it is known that Epodyl acts locally on bladder tumours, the mode of its action is uncertain. This animal experiment was designed as part of a project intended to determine the effect of the drug on bladder tumours. The project consists of several parts, including (i) a study of the effects of Epodyl on animal and human tumour cells observed *in vitro*, using different concentrations at different temperatures, and comparing the changes with those produced by water and 0.9% saline; (ii) a study of the effects of Epodyl on standard implanted animal sarcomas; and (iii) an attempt to induce growth of human and animal tumours in animal bladders, so that when tumour had been induced, the effects of Epodyl could be observed.

The experiments described here consist of only the first part of the third section of the project—the induction of tumour growth in animal bladders.

Materials and Methods

Female Sprague-Dawley rats of approximately 350 g weight, and female New Zealand White rabbits of approximately 2.5 kg weight, were chosen for the experiments. The tumours selected for implantation in the 2 species were Walker sarcoma for rats and Vx2 sarcoma for rabbits (Smith *et al.*, 1952).

Tumour suspensions were prepared using a standard cell separation unit. The cells were suspended in nutrient medium and diluted so that a Coulter count after staining with Methylene Blue showed a viable cell count of 250,000 per mm^3.

The animals were anaesthetised with ether, and unconciousness maintained with open ether inhalation. Following anterior urethrotomy as far as the genu, a 2 Ch epidural cannula was passed into the bladder *per urethram*. We found it difficult to catheterise the animals without urethrotomy. The bladder was emptied, and then filled with Cetavlon (ICI)—the rat bladders held approximately 0.5 ml and the rabbit bladders approximately 10 ml. The Cetavlon was left in the bladder for 30 min.

Some animals were sacrificed at this stage. In the other animals the Cetavlon was withdrawn and the bladder irrigated with 0.9% saline before injecting tumour suspension to fill the bladder. These animals were allowed to recover, and sacrificed at 7 days: in the event of death before this time, autopsy was performed.

Results

Four animals of each species were used for the initial acute experiment. In all cases we found

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that the normal transitional cell lining of the bladder had undergone considerable change: the epithelium was hyperaemic, and often lifted away from the submucosa by oedema fluid. There was patchy detachment of clumps of cells, leaving the submucosal layer bare. There was considerable submucosal vascular congestion and haemorrhage.

Two of the 6 rabbits used for the second part of the experiment died before recovery, and 1 shortly afterwards. In the remaining 3, all surviving to 7 days, tumour was found in the bladder at autopsy. The plaques of tumour were small, and mainly sub-epithelial.

Ten rats were used for the second part. Two died before recovery. Another 2 died within 3 days of operation and in all these cases death was caused by peritonitis secondary to rupture of acutely necrosed bladders. In the remaining 6 animals, viable tumour was found under the mucosa in the bladders of all of them: the size of the tumour varied from small plaques some 2 mm in diameter to a mass almost filling the bladder in one animal (Fig.).

Tumour was also found in one or both kidneys of 3 of the 6 rats showing tumour in the bladder. In these 3 cases there were white plaques of tumour on the surface of the kidney, and in one case the lower pole of the right kidney was mainly replaced by tumour. Microscopy showed tumour cells in the distal tubules, and at higher levels, almost to the glomeruli.

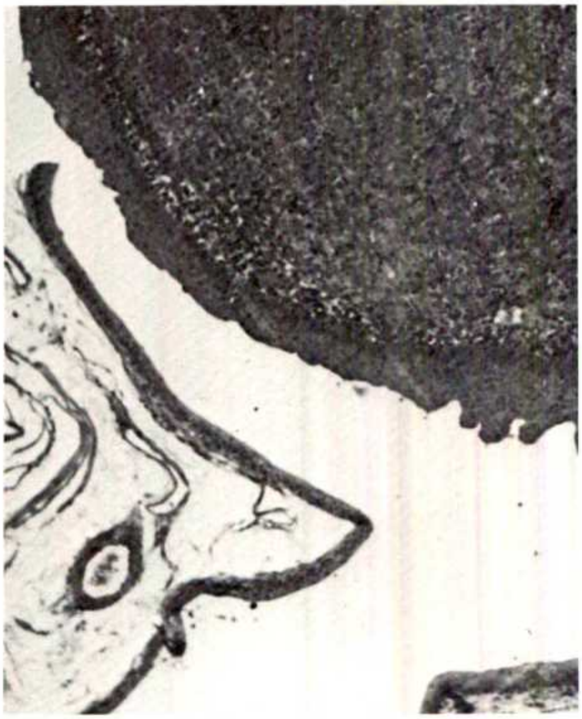

Fig. Walker tumour induced in rat bladder.

Further Procedures

In order to determine the cause of the different behaviour of tumour in the 2 species, with regard to induction of tumour in the kidneys as well as in the bladders in rats, 2 further acute experiments were designed.

Two animals from each species were used for the first. The animals were anaesthetised and positioned as before, and catheterised. A midline laparotomy from xiphisternum to symphysis pubis was performed, and the viscera displaced in such a way as to expose the whole of the urinary tract. Methylene blue was injected into the bladder: vesicoureteric reflux was seen in the rats, but not in the rabbits. As a check, the kidneys of the rabbits were injected with the dye, which passed freely down the ureters to the bladder.

Secondly, standard cystograms were carried out, using barium suspension. Reflux was confirmed in the rats, and similarly its absence in the rabbits.

As a final check on the validity of the results of our tumour implantation experiment, 5 animals of each species had tumour suspension injected into the bladder without previous irrigation with Cetavlon. In no case did tumour develop.

Discussion

Our results show that it is relatively simple to induce tumour growth in animal bladders, but only if cystitis has been induced with an irritant chemical. At the same time, if reflux occurs, it is possible to induce tumour growth in the kidney.

Cetavlon is occasionally used as an antiseptic for bladder irrigations. Our animal work shows that it rapidly induced a severe cystitis. If cystitis, whether chemical or bacterial, is conducive to tumour implantation, should we be more cautious with regard to the presence of infections in the patients we regularly treat for recurrent bladder tumour? If a patient with a bladder tumour has reflux—reflux which may have been caused by radical endoscopic resection of a tumour adjacent to a ureteric orifice—should the possibility of retrograde tumour implantation be considered?

While the "field of growth" theory of urothelial tumour development is well established, is there a possibility that some upper tract tumours arising subsequent to initial bladder lesions may have arisen retrogradely in the way we have demonstrated?

From the point of view of the Epodyl project, the tumours we selected were mesothelial in origin, and implanted deep to the epithelium. They could not be exposed to Epodyl, but we are pursuing our studies with other tumours.

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The Pseudo-obstructed Bladder in Enuretic Children

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Summary—In a minority of enuretic children with severe day symptoms, and especially when there is urinary infection, there are bladder diverticula and trabeculation and possibly also harmful vesicoureteric reflux which suggest the presence of an infravesical obstruction. However, in 11 children with this syndrome who underwent urodynamic studies, no anatomical or functional obstruction was demonstrable. It is contended that the obstructive signs are the result of uninhibited detrusor contractions being voluntarily resisted by contraction of the external urethral sphincter so that abnormally high intravesical pressures result.

Management involves the use of detrusor-inhibitory drugs. Ureteric reimplantation may be needed for reflux. In the majority of cases symptoms improve with time but the bladder diverticula persist.

The majority of enuretic children, with or without daytime symptoms of frequency, urgency and urge incontinence, show no abnormality on clinical examination; the urine is sterile and routine urological investigations reveal no causative urinary tract pathology. However, in a minority with the same symptomatology the urine is commonly infected and, although the bladder empties completely, urography and endoscopy demonstrate features suggestive of an infravesical obstruction. Bladder trabeculation and diverticula exist and vesicoureteric reflux may be present or develop with time so that ascending infection, pyelonephritic scarring and failure of kidney growth may result. In order to determine the nature of the aetiological factors involved, 11 children with this syndrome underwent urological and urodynamic investigations.

Patients and Methods

The patients consisted of 4 boys and 7 girls ranging in age at the time of presentation from 3 to 10 years. In all except one the urine was infected, either with *E. coli* or with *Klebsiella*. Investigations consisted, in all cases, of intravenous urography, micturating cystourethrography, endoscopy, measurement of the maximal urinary flow rate and the urethral pressure profile, cystometrography and, in girls, calibration of the distal urethra. In 4 children the activity of the voluntary urethral sphincter was studied by electromyography. In our experience there is a limit to the urodynamic studies one can usefully perform in young children. Painful manoeuvres have to be avoided, not only for obvious humanitarian reasons but because they can be self-defeating. When the patient is hurt, his co-operation is lost and further investigation becomes impossible. For this reason, general anaesthesia was always employed for endoscopy and urethral pressure profilometry and sphincter electromyography were carried out with the child asleep under nitrous oxide and oxygen.

Results

Intravenous urography showed no upper tract dilatation in any patient; in 4, one kidney was small, with the features of pyelonephritic atrophy (Figs. 1 and 2). Micturating cystourethrography demonstrated bilateral or multiple diverticula in all cases; in each the bladder emptied completely, leaving residue in the diverticula (Figs. 1, 2, 3 and 4). Unilateral vesicoureteric reflux was present at the initial examination in 2 patients (Figs. 2 and 3); in one girl reflux, absent at the first investigation, developed later. In the one patient in whom reflux was not treated surgically it stopped spontaneously with resolution of the symptoms (Fig. 3). Urethrography in boys demonstrated no urethral obstruction. In some of the girls the urethrogram had the appearance of the "spinning-top" urethra (Fig. 4). However, in none was there any significant

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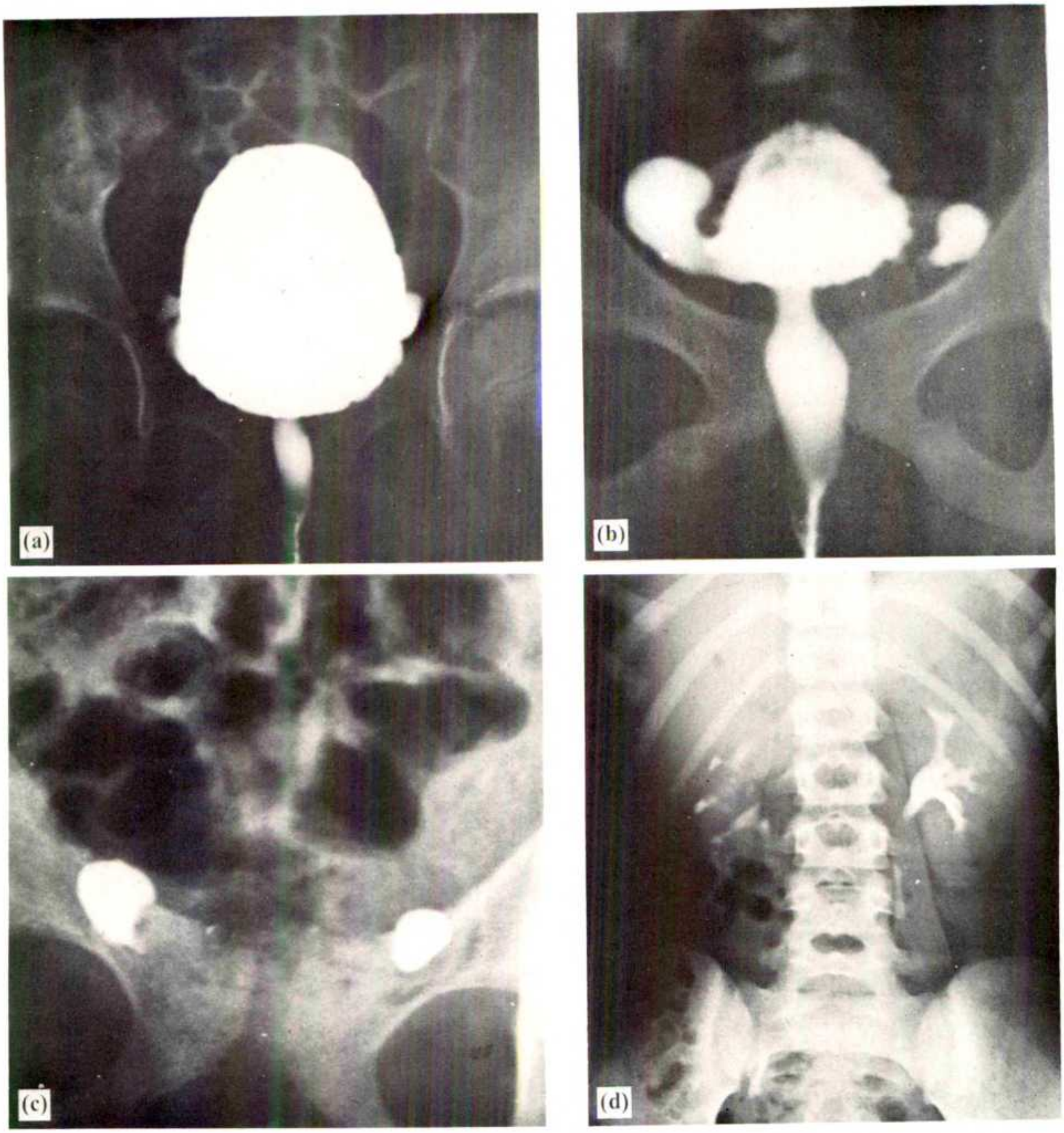

Fig. 1 Micturating cystourethrogram (MCU) and IVP in 8-year-old enuretic girl with day symptoms and urinary infection. (a) MCU. Early voiding phase. Mild bladder trabeculation. Bilateral diverticula. (b) MCU. Mid-voiding phase. Diverticula more prominent. (c) MCU. After voiding. Bladder empty. Residue in diverticula. No reflux. (d) IVP. Small, scarred right kidney. Hypertrophied left kidney.

narrowing at or near the urethral meatus on instrumentation. Endoscopy revealed, in all cases, the vesical diverticula and mild to moderate bladder trabeculation. Cystitis cystica was evident in 4. The maximal urinary flow rate ranged from 17 ml/sec in a 4-year-old boy to 44 ml/sec in a 10-year-old girl. Urethral profilometry demonstrated pressures between 30 cm H_2O in a 7-year-old boy

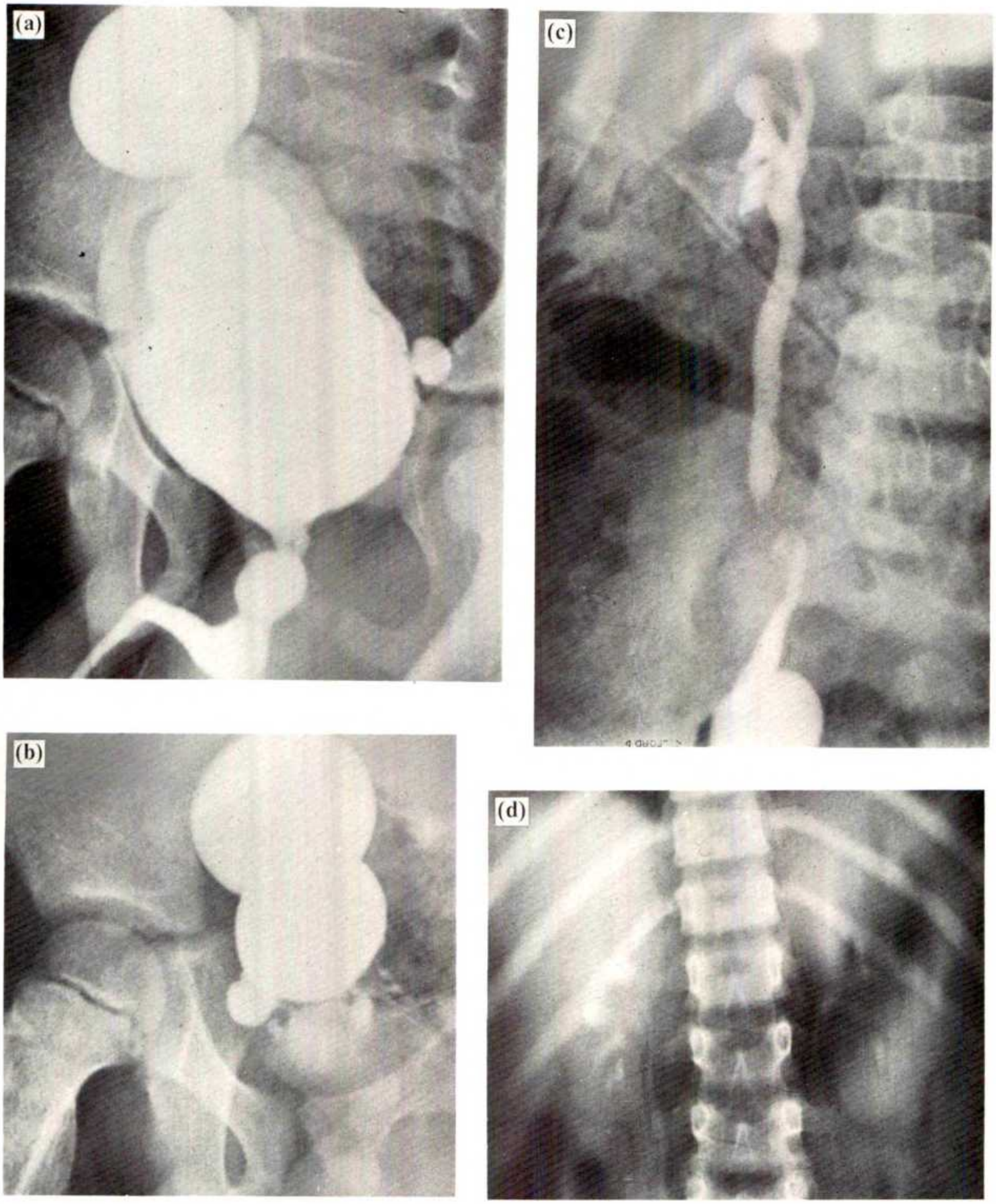

Fig. 2 MCU AND IVP in 9-year-old enuretic boy with day symptoms and urinary infection. (a) MCU. Several bladder diverticula. No urethral obstruction. (b) MCU. After voiding. Bladder empty. Residue in diverticula. (c) MCU. Reflux to right kidney. (d) IVP. Right kidney small and scarred. Left kidney normal.

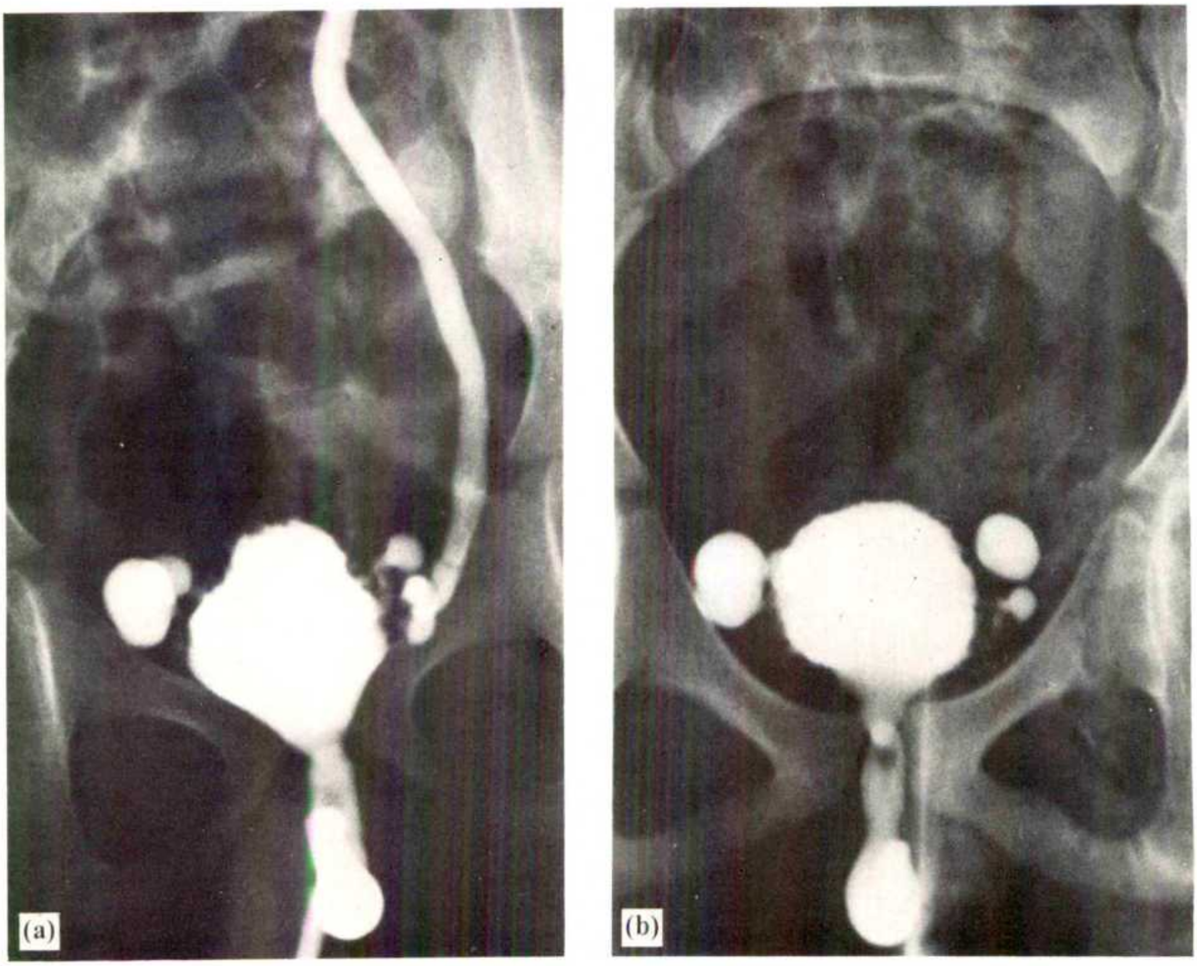

Fig. 3 MCUs in boy with uninhibited bladder. (a) Aged 3 years when symptomatic and urine infected. Multiple bladder diverticula and left-sided reflux. (b) Aged 7 years when symptomless and urine sterile. Bladder diverticula persist. Reflux has stopped spontaneously.

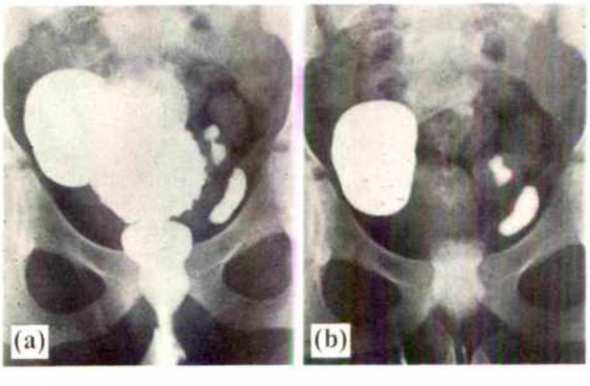

Fig. 4 MCU in 10-year-old enuretic girl with day symptoms and urinary infection. (a) During voiding. Multiple bladder diverticula. "Spinning top" urethrogram. (b) After voiding. Bladder empty. Residue in diverticula.

to 54 cm H_2O in a 9-year-old girl. Cystometry showed, in all cases, an unstable bladder of low capacity with uninhibited detrusor contractions at small volumes. Electromyography of the external urethral sphincter was performed simultaneously with cystometry in 4 patients; in each the sphincter relaxed completely during a voiding detrusor contraction.

Discussion

Although the pathological changes in the bladder in the children studied were those generally considered to be pathognomonic of obstructive uropathy, the facts that the bladder emptied completely in all cases and that the maximal flow rates were at normal or even above normal levels tend to refute the existence of an abnormally high resistance to urethral flow. Also, we have failed to demonstrate any anatomical or functional urethral obstruction. The absence of the latter was indicated by the normal findings at urethral pressure profilometry and by electromyography, which demonstrated complete relaxation of the external sphincter during a voiding detrusor contraction and so denied the existence of detrusor-sphincter dyssynergia. In the boys, urethrography and urethroscopy revealed no structural abnormality. In some of the girls urethrography showed various degrees of the "spinning-top" urethra (Fig. 4). Such a urethrogram has been considered by some authors (Lyon and Tanagho, 1965) to be indicative of distal urethral stenosis, but the diagnosis of this lesion lacks precision since there is no agreement as to the range of normality in the calibre of the lower urethra in girls (Graham *et al.*, 1967). In none of our cases could any unequivocal urethral narrowing be demonstrated by instrumentation and therapeutic urethral dilatation, performed empirically at the conclusion of endoscopy in 4 girls, did not produce any symptomatic improvement. We believe the "spinning-top" urethrogram to be a normal radiological appearance caused by differing degrees of distensibility in different parts of the female urethra during a rapid urinary flow.

It is our contention that, regardless of the bladder changes, these children have no obstruction to voiding. The basic lesion is the unstable bladder, with infection as a secondary, exacerbating factor. When an uninhibited detrusor contraction occurs the child resists the sudden, unexpected urge to void by producing a strong voluntary contraction of the external sphincter. Little girls often supplement the sphincter contraction by squatting on the heel, which inhibits voiding by compressing the perineum and preventing descent of the bladder base (Vincent, 1966). The effect of the voluntarily resisted detrusor contraction is an abnormally high intravesical pressure which persists until either the detrusor relaxes or the volume of the bladder content is reduced by urinary leakage or by micturition. Ultimately such pressure rises, frequently repeated, produce the bladder changes found.

The bladder instability is best regarded as being due to immaturity of vesicourethral function. The precise neurological or neuromuscular mechanisms involved in the development of bladder control during early childhood are unknown but the concept that normal maturation is delayed in enuretic children is substantiated by the fact that, with time, the symptoms improve and cease altogether in the great majority of cases.

Unilateral vesicoureteric reflux was found in 3 children in our series; in one of these the related kidney showed pyelonephritic atrophy (Fig. 2). In 3 other cases pyelography showed unilateral renal scarring but reflux was not demonstrated (Fig. 1); however, the appearances suggested that reflux had been present previously but had undergone spontaneous cure. Spontaneous cessation of reflux was seen to occur in one boy when bladder function became normal, even though the diverticula persisted (Fig. 3). In one girl reflux was not present initially but appeared later, suggesting that its development was secondary to the vesical dysfunction and not due to a primary anomaly of the ureteric insertion.

In the treatment of children with this syndrome, infection must be controlled by chemotherapy. Symptomatic management of the uninhibited bladder is difficult in the short term. We have found that the best results were obtained with propantheline bromide (Probanthine) but the drug may have to be given in high doses, almost to the point of producing such side effects as dryness of the mouth and dilated pupils. In other cases dicyclomine hydrochloride (Merbentyl) or emepronium bromide (Cetiprin) may be more effective. Hydrostatic distension of the bladder under anaesthesia was performed on 2 of our patients but no lengthy improvement resulted. The symptomatology improves with time and in 5 of our cases bladder function ultimately became normal although the diverticula persisted.

Since vesicoureteric reflux may halt spontaneously with improvement in vesical function, the operative cure of reflux is indicated only when there is clinical or radiological evidence or suggestion of renal damage. Ureteric reimplantation was performed in 2 patients in our series. The diverticula are seldom sufficiently large to warrant excision on their own account; in one of our cases diverticulectomy was performed at the same time as ureteric reimplantation (Fig. 2).

We believe it is important to recognise this group of patients and that the enuretic child with severe day symptoms, especially when there is urinary infection, does, unlike most bed wetters, warrant urological investigation. The bladder changes themselves seldom call for treatment other than that one would employ with the usual enuretic, but harmful reflux may exist or develop and require operative intervention. Also, it is important to realise that these children do not have any infravesical obstruction to micturition and that there is no indication for widening or resecting the bladder neck or for urethral manoeuvres such as dilatation or urethrotomy or the fulguration of imaginary urethral valves.

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Results of Caecocystoplasty for Tuberculous Bladder Contracture

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Summary—The results of caecocystoplasty for tuberculous bladder contracture in 30 patients over a 15-year period are presented. The operative mortality was 3.3%. Poor renal function was not a contraindication to surgery.

The results indicate that caecocystoplasty provided relief of symptoms in over 90% of patients. Renal function was preserved and associated obstructive uropathy was usually relieved. Efficient cystoplasty emptying was observed in 80% of patients if detrusor resection was kept to the minimum consistent with a wide caecovesical anastomosis.

The caecum was first used in urological surgery as a bladder substitute by Verhoogen in 1908; the technique included the formation of a fistula between the skin and the appendix to allow intermittent catheterisation of the caecal reservoir.

Couvelaire was the first to advocate the use of the caecum in bladder reconstruction and published an account of 3 caecocystoplasties in 1950. Gil-Vernet and Adan (1956) and Gil-Vernet (1965) described its use for bladder augmentation and stressed the protection afforded by the ileocaecal valve against reflux into a ureter implanted into the adjacent ileum. Turner-Warwick and Ashken (1967) described their experience and advocated the use of the caecum because it was easily mobilised, required no refashioning and had ample blood supply.

This paper describes the long-term results of caecocystoplasty for tuberculous bladder contracture in 30 patients.

Patients and Procedures

Thirty patients with tuberculous bladder contracture underwent caecocystoplasty between 1963 and 1978. Thirteen were male and 17 were female. Their ages at presentation, the incidence of presenting symptoms and the pre-operative urographic appearances are shown in Tables 1, 2 and 3.

All the patients received the standard course of therapy in use at that time, following the isolation of *Myco. tuberculosis* from the urine. This regime, combined with excisional surgery when indicated, resulted in the elimination of the organism from the urine in all cases. Bladder symptoms were improved temporarily in 3 patients following the introduction of chemotherapy but in the remaining cases the symptoms were unchanged by both chemotherapy and excisional surgery.

Table 1 Age at Presentation (30 patients)

17-30 years	9 patients
30-50 years	14 patients
50-70	7 patients

The pre-operative bladder capacities are shown in Table 4. Bladder fibrosis and mucosal vegetations were observed cystoscopically in all patients at presentation and were completely unaffected by excisional surgery and long-term chemotherapy. Endoscopic cauterisation of vegetations and bladder instillations were used over long periods in 4 patients with no improvement.

Table 2 Presenting Symptoms (30 patients)

Increased frequency	*Patients*
Diurnal	
¼-1 hourly	14
1-2 hourly	10
2-3 hourly	6
Nocturnal	
4-12 times	19
1-3 times	11
Scalding	19
Haematuria	13
Loin pain	7
Enuresis	3

Read at the 34th Annual Meeting of the British Association of Urological Surgeons in Brighton, June 1978.

Table 3 Pre-operative Urographic Assessment (30 patients)

Urographic appearance	*Patients*
Poor	
Bilateral severe disease Bilateral hydronephrosis Severe disease in a solitary kidney Hydronephrosis in a solitary kidney	17
Adequate:	
Solitary normal kidney Solitary slightly diseased kidney	10
Good:	
One kidney normal, other kidney diseased or hydronephrotic	3

Surgical Technique

Pre-operative bowel preparation consisted of either oral neomycin or streptomycin 1 g 8-hourly for 48 h before surgery together with colonic washouts using a sulphonamide solution.

Laparotomy was performed through a lower right or left paramedian incision. The caecum was grasped and drawn down into the pelvis to confirm adequate mobility of the ileocolic segment. The caecum, ascending colon and hepatic flexure were then mobilised and, after appendicectomy, the ileocaecal segment was isolated with its mesentery and the ileal stump closed. For bilateral or left-sided ureteric reimplantation into the ileal portion of the segment 30 cm of ileum were included in the segment. With no reimplantation or with right-sided ureteric reimplantation 8 cm of ileum were included. Direct mucosa-to-mucosa implantation was used when the ureter was rigid and dilated; otherwise a cuffed-nipple technique was employed. Intestinal continuity was restored by end-to-side ileocolic anastomosis.

The fundus of the bladder was resected after reflection of overlying peritoneum. The aim of this resection was a wide vesical stoma but as much bladder as possible was conserved.

Ureteric reimplantation, if required, was best performed before caecovesical anastomosis; otherwise technical difficulties were formidable. The caecum was then rotated through 180° and its open end was anastomosed in 2 layers to the bladder remnant using 2/0 chromic catgut sutures. More recently "Dexon" sutures have been preferred. The peritoneal flaps were then sewn to the base of the cystoplasty for further protection of the anastomosis.

Table 4 Pre-operative Bladder Capacities (30 patients)

Capacity (ml)	*Patients*
30-100	9
100-200	15
200-300	6

Table 5 Duration of Post-operative Follow-up (30 patients)

Up to 1 year	5 patients
1-5 years	13 patients
5-15 years	12 patients

The wound was closed in layers with drainage to all anastomoses. A balloon catheter was left *in situ* for 10 days.

Patient Follow-up

All surviving patients have been reviewed at 6-monthly to yearly intervals to elicit progress of symptoms, renal function, urography, cystoscopic appearance and volume of residual urine. The duration of follow-up is shown in Table 5.

Urodynamic Evaluation

In 23 patients pressure-flow studies have been performed post-operatively using Disa Urodynamic measuring equipment. These studies were combined with synchronous videocystography. Flow curves were obtained after spontaneous diuresis and after filling with Urografin 30%. Residual urine was measured before filling with Urografin 30%. Intravesical (cystoplasty) pressure was recorded via a transurethral 1 mm diameter PTFE catheter. Abdominal (rectal) pressure was recorded via a rectal 2 mm PTFE catheter covered with a finger stall. Methods, definitions and units conform to the standards proposed by the International Continence Society except where specifically noted.

Results

Five patients have died and Table 6 gives the causes of death and times of death following cystoplasty. The operative mortality was 3.3%, representing one early patient who died with a faecal fistula and peritonitis. Two patients (A.G. and J.C.) died from renal failure 15 months and 2 years after operation. Cystoplasty provided relief of symptoms in these patients but failed to reverse the progressive deterioration in renal function observed before operation. In retrospect

Table 6 Analysis of Mortality

Age of patient	*Cause of death*	*Time of death after cystoplasty*
58	Faecal fistula	4 weeks
64	Ruptured aortic aneurysm	6 weeks
57	Renal failure	15 months
66	Myocardial infarction	2 years
48	Renal failure	5 years

it is clear that cystoplasty outflow obstruction was a significant factor in the deterioration in both patients.

Post-operative complications are shown in Table 7. External urinary fistulae caused most problems but all healed with catheter drainage within 3 weeks. In one patient leakage at a ureteroileal anastomosis required re-exploration and resuture. Three male patients required post-operative transurethral prostatectomy before efficient cystoplasty emptying was achieved. All 3 were over 45 years of age and were the only patients in the series with prostatic calcification on plain X-ray. Two female patients required internal urethrotomy to achieve efficient cystoplasty emptying. One male patient required bladder neck resection. Contraction of the caecovesical anastomosis with delay in caecal pouch emptying has occurred in one patient who is under careful observation.

The progress of symptoms in the 29 patients who left hospital is shown in Table 8. Relief of diurnal frequency was invariable but did not fully develop until 3 to 6 months after operation. Symptomatic improvement correlated with the observed increase in bladder capacity obtained by operation (Table 9).

The progress of urography in the 29 patients who left hospital is shown in Table 10. There has been a satisfactory improvement in renal function in some cases and renal insufficiency has not proved to be a contraindication to the operation (Table 11).

Table 7 Post-operative Complications

Faecal fistula	1
External urinary fistula	7
Wound disruption	2
Incisional hernia	4
Intestinal obstruction from adhesions	1
Bladder outflow obstruction	6
Contraction of cystoplasty anastomosis	1
Stenosis of ureteric implant	1
Enuresis	10

Table 8 Progress of Symptoms After Caecocystoplasty (29 patients)

	Pre-operative	*Post-operative*
Frequency		
¼-1 hour	14	—
1-2 hours	19	—
2-3 hours	5	11
3-4 hours	—	18
Nocturia		
×4-12	19	2
×1-3	10	21
Absent	—	6
Enuresis	3	10
Scalding	19	2
Haematuria	13	—
Loin pain	6	—

The incidence of post-operative reflux in 26 of the patients was assessed by cystography (Table 12). The reflux protection offered by a cuffed-nipple ureteroileal anastomosis could, of necessity, only be assessed in the 5 patients with ileocaecal valve incompetence. Free reflux of contrast material to the kidney occurred through 3 out of the 5 nipple anastomoses in these 5 patients.

The 23 patients assessed by videocystography combined with a pressure-flow study were separated on clinical grounds into 3 groups (Table 13).

The results of the pressure-flow studies in the symptom free group are shown in Table 14, in the obstructed group in Table 15 and in the enuretic group in Table 16. Videocystourethrography gave reliable information on the presence of reflux, cystoplasty function and the presence of bladder neck obstruction. Obstruction at the distal urethral segment level was not observed.

Discussion

Surgical Technique

A radical detrusor resection extending to the trigone has been advocated at cystoplasty by many authors (Couvelaire, 1950; Cibert, 1953; Gil-Vernet and Gosalvez, 1957; Turner-Warwick and Ashken, 1967; Charghi *et al.*, 1967). Without

Table 9 Pre-operative and Post-operative Bladder Capacity (29 patients)

Capacity (ml)	*Pre-operative*	*Post-operative*
30-100	9	—
100-200	14	—
200-300	6	1
300-500	—	24
500-700	—	4

Table 10 Progress of Urography in the 40 Functioning Kidneys (29 patients)

	Pre-operative	*Post-operative*
Normal kidney	16	23
Moderate hydronephrosis	—	9
Gross hydronephrosis	24	8

such a resection, contraction at the enterovesical anastomosis was judged inevitable, resulting in conversion of the cystoplasty to a non-functioning diverticulum. Hanley (1959) and more recently Smith *et al.* (1977) have challenged this view. The results of this study suggest that as much of the bladder wall as possible should be conserved at operation consistent with an anastomosis of 5 cm or so in diameter. With this approach cystoplasty was technically much easier and the voiding pattern in the majority of cases was excellent. Contraction of the caecovesical anastomosis occurred in only one case and this was judged to be due to faulty operative technique. The ileocaecal valve prevented retrograde reflux of urine in 64% of cases. However, in order to protect the 36% of cases with ileocaecal valve incompetence a reflux preventing technique of ureteroileal anastomosis is required. In this context a cuffed-nipple anastomosis proved unsatisfactory and it is suggested that a tunnel type anastomosis might be better.

The operative mortality is acceptable although the death should have been prevented. The high incidence of urinary fistulae is unacceptable and has been improved by 2-layer closure with Dexon. Turner-Warwick and Ashken (1967) reported a relative outflow obstruction in two-thirds of a group of patients who had undergone caecal bladder substitution rather than enlargement. Other authors have reported a lower incidence of outflow obstruction following cystoplasty (Gil-Vernet, 1965; Duff *et al.*, 1970). In our series 6 patients (20%) developed a degree of chronic retention due to obstruction at bladder neck level. Relief was obtained in all cases by endoscopic resection in the male or urethrotomy in the female. If the 3 male patients with prostatic calcification and adenoma formation are excluded, then the incidence of chronic retention in the series as a whole is 10%. This low incidence of impaired emptying is probably related to our deliberate preservation of as much detrusor as possible.

Table 11 Progress of Renal Function (29 patients)

	Pre-operative	*Post-operative*
Creatinine clearance:		
More than 100 ml/min	12	16
50-100 ml/min	8	11
Less than 50 ml/min	9	2

Table 12 Incidence of Post-operative Reflux (26 patients assessed by cystography)

Caecocystoplasty (ureters left *in situ*)
12 Patients—vesicoureteric reflux in 3 patients before operation; no change after operation.
Ureteroileocaecocystoplasty
14 Patients < Ileocaecal valve competent (9 patients)
Ileocaecal valve incompetent (5 patients)

Küss *et al.* (1970) noted a 12% incidence of diurnal incontinence and an 18% incidence of enuresis post-operatively, while Charghi *et al.* (1967) reported enuresis in 27% of their patients post-operatively, but a large number of these were transient. In our series 10 patients noted enuresis during the post-operative period but in no case did diurnal incontinence occur. In 5 the enuresis resolved. Three of the remaining 5 patients had enuresis before cystoplasty.

All the patients had very severe symptoms prior to cystoplasty. Frequency was reduced to 3-hourly or less in all patients and all were delighted with the result.

There have been few well documented reports concerning renal function following enterocystoplasty. Hanley (1959) reviewed renal progress over a 5-year period in 31 ileocystoplasty patients and found no increase in renal damage. Gil-Vernet *et al.* (1962a) found no important disturbance in blood chemistry over a 3-year period in 41 bladder substitute patients. In our series 7 patients with initially poor renal function showed a definite improvement. Our results are at variance with those of Smith *et al.* (1977) who stated that chronic renal insufficiency was a contraindication to caecocystoplasty and that a creatinine clearance of at least 40 ml/min was mandatory for any enterocystoplasty, but confirm those of Küss

Table 13 Patient Groups assessed Urodynamically (23 patients)

(A) Sympton-free group Residual urine < 50 ml	13
(B) Obstructed group Residual urine > 100 ml	4
(C) Enuretic group Residual urine < 50 ml	6

Table 14 Results of Pressure Studies in the Symptom-free Patients (13 patients)

	Mean value	*Range*
Residual urine (ml)	30	0-50
First sensation (ml)	250	100-300
Cystoplasty capacity (ml)	400	300-500
Maximum cystoplasty pressure (voiding) (cm H_2O)	17	1-36
Maximum abdominal pressure (voiding) (cm H_2O)	57	17-80
Maximum flow rate (ml/s)	15	10-21
Flow duration (s)	53	10-120

Table 16 Results of Pressure Studies in the Enuretic Patients (6 patients)

	Mean value	*Range*
Residual urine (ml)	24	0-50
First sensation (ml)	230	100-400
Cystoplasty capacity (ml)	360	200-600
Maximum cystoplasty pressure (voiding) (cm H_2O)	16	5-24
Maximum abdominal pressure (voiding) (cm H_2O)	68	50-90
Maximum flow rate (ml/s)	14	9-20
Flow duration (s)	46	10-120

et al. (1970) who stated that patients with a creatinine clearance of over 15 ml/min are acceptable.

The urodynamics of enterocystoplasties were studied by Gil-Vernet *et al.* (1962b) who reported peristaltic contractions with raised intrinsic cystoplasty pressure during voiding. These pressures were over and above the abdominal pressure from straining employed during voiding. Turner-Warwick and Ashken (1967) found cystoplasty segments to be relatively weak when compared to a normal detrusor. During filling, typical bowel contractions were noted which diminished during voiding to such an extent that the patient had to complete evacuation using abdominal straining. In all patients urinary flow was slow and intermittent.

The results of pressure-flow videocystography in this series confirm Turner-Warwick and Ashken's (1967) finding that the expulsive force during voiding is almost entirely due to abdominal wall contractions. The cystoplasty itself generates only brief low pressure and ineffective contractions.

In several cases at cystography a transfer of contrast medium from the bladder remnant to the caecal segment was observed immediately prior to voiding. This appeared to be due to active bladder remnant contraction and was associated with funnelling of the bladder neck. Abdominal straining was required to initiate and maintain voiding in all cases but bladder remnant contraction, when it occurred, was associated with the most efficient voiding patterns in the group as a whole. Urodynamic evaluation did not reveal any significant difference between the symptom-free and the enuretic cystoplasty patients. The characteristic features of the "obstructed" patients were a large residual urine, a higher total capacity and pronounced caecal peristaltic contractions at total capacity.

Table 15 Results of Pressure Studies in the Obstructed Patient (4 patients)

	Mean	*Range*
Residual urine (ml)	210	100-500
First sensation (ml)	400	250-650
Cystoplasty capacity (ml)	600	550-700
Maximum cystoplasty pressure (voiding) (cm H_2O)	15	5-35
Maximum abdominal pressure (voiding) (cm H_2O)	73	60-110
Maximum flow rate (ml/s)	11	6-16
Flow duration (s)	90	30-130

This study has shown that caecocystoplasty for tuberculous bladder contracture is a satisfactory procedure producing relief of symptoms in over 90% of patients. Renal function is usually preserved. The ileocaecal valve is important in preventing ileoureteric reflux but a tunnel-type antireflux procedure is recommended when anastomosing the ureters to the ileum. The bladder remnant should be as large as possible and the anastomosis between the caecum and the bladder as wide as can be obtained.

The caecal remnant is essentially passive during voiding which is achieved using abdominal straining.

Cystoplasty function should be assessed regularly by cystourethrography. If emptying is seen to be inadequate transurethral resection in the male or urethral overdilatation or urethrotomy in the female is indicated. The success of any urethral surgery in lowering urethral resistance and eliminating residual urine should be confirmed by post-operative cystourethrography. Routine urodynamic tests, although of interest from the research aspect, are of little practical value in the management of patients treated by caecocystoplasty.

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The Late Symptomatic and Functional Results of Enterocystoplasty

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Summary—A symptomatic and, where possible, urodynamic assessment has been made in 19 patients undergoing enterocystoplasty over a 16-year period. It is suggested that this operation should be considered in those cases of interstitial cystitis and irritable bladder syndrome in which all recognised medical and surgical treatment has failed.

Enhancing bladder capacity by the addition of an isolated segment of bowel is not a new concept. The operation has been performed for a variety of clinical conditions reflecting the changing nature of urinary tract pathology over the years. This paper analyses the experience of this operation in our urological departments over a 16-year period and examines current criteria for patient selection and results of operative procedures.

Patients and Methods

Nineteen patients, 15 male and 4 female, aged 13 to 74 years (mean 38.8 years), were operated upon between 1961 and 1977. The main condition for which the operation was performed was the irritable bladder syndrome (Table 1). This term describes patients in whom symptoms of frequency, urgency, urge incontinence and often enuresis are associated with an unstable bladder demonstrated on inflow cystometry during urodynamic assessment. Of the remaining conditions, tuberculous systolic bladder has not been treated in this way since 1969. The 3 operations performed between 1961 and 1966 for residual post-radiotherapy carcinoma of fundus of bladder and the single operation for post-radiotherapy contracted bladder were all unsuccessful and no similar cases have been treated by cystoplasty since that time.

Table 1 Pre-operative Diagnosis

TB systolic bladder	2
Carcinoma of bladder	3
Post DXR contracted bladder	1
Interstitial cystitis	3
Irritable bladder syndrome	10
	19

Prolonged bladder distension therapy has replaced enterocystoplasty as our treatment of choice for interstitial cystitis since 1972 (Dunn *et al.*, 1977).

Symptoms were the principal indication for operation. These consisted of severe frequency and nocturia, lifelong enuresis occurring more than 4 times per week, pain, and urgency usually combined with incontinence. One or more of these principal symptom-complexes was present in each patient and they are detailed in Table 2. It should be stressed that all these symptoms were of a severe degree, and sufficient to seriously affect both the working and social life of the patient.

Table 2 Principal Symptom-complexes for which Operation performed

1	Severe frequency and nocturia	15
2	Enuresis	7
3	Bladder pain	5
4	Urgency/incontinence	7

In 10 patients with the irritable bladder syndrome the symptoms were often lifelong, and present in all cases prior to surgery for more than 10 years. In the remaining 9 patients the operation was performed within 5 years of presentation. The patients with irritable bladder syndrome had had severe symptoms for many years and as a consequence had undergone numerous and detailed investigations. In none was any disturbance of renal function detected and in all other aspects they were fit and healthy. A wide variety of general

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measures, including fluid restriction and voiding discipline, had been tried without success. Similarly, multiple drug therapy had been given, again with no significant relief of symptoms. In addition, the patients with irritable bladder syndrome had previously undergone different surgical procedures in an attempt to alleviate their suffering. These procedures included hydrostatic bladder dilatation, Helmstein's prolonged bladder distension, sacral denervation and, in 3 cases operated upon at a much earlier date, transurethral surgery to the prostate and bladder neck. None of these surgical manoeuvres was successful.

Physical examination was normal except in the patients with tumour, who all had a mass on pelvic examination. Pre-operative investigations, including haemoglobin, urea and electrolytes and urine culture, were normal. Intravenous urography was abnormal only in the 3 patients with tumour.

Cystoscopy again revealed the presence of tumour in these 3 patients, but also showed marked trabeculation in 7 patients with a diagnosis of irritable bladder syndrome. Urodynamic studies were performed pre-operatively in 8 patients and the results will be discussed below in relation to the post-operative assessment.

The operative procedures are shown in Table 3. In 13 patients no bladder muscle was excised but recently there has been a tendency to excise bladder tissue so as to leave only a cuff around the trigone and bladder neck.

Table 3 Operative Procedures

Ileocystoplasty with "cow's horn"	2
Caecocystoplasty	5
Colocystoplasty with "patch"	7
Colocystoplasty with "helmet"	5
	19

The ideal objective assessment for this operation involves urodynamic studies. However, this investigation has only been available for the past 6 years and was therefore performed pre-operatively in only 8 of the 19 cases. An attempt was made to obtain post-operative urodynamic information on 15 patients. Eight patients, including 2 who had had pre-operative studies, refused outright and one patient declined on the grounds that he was so well that he did not want to jeopardise his present well-being. This left 6 patients in whom both pre-operative and post-operative studies were performed. Two cases were of interstitial cystitis and 4 of irritable bladder syndrome.

Results

The results of surgery have been based partly on subjective assessment by the patient. This is inevitable since the operation was performed primarily to relieve symptoms. Thus patients were asked to assess the relief of symptoms in the 4 pre-operative symptom-complexes of frequency and nocturia, enuresis, pain and urgency with urge incontinence. Those who maintained that the operation had brought them significant relief of symptoms in the various groups are classed as "cured". Those with less symptomatic relief are graded as better, the same or worse. It is stressed that "cured" does not imply a complete return to normality, but indicates that the patient is able to lead a reasonable working and social life. The results based on the purely subjective analysis are shown in Table 4. Although the 3 patients with tumour were dead within 12 months from local and metastatic carcinoma, they were initially assessed with the other 16 patients. These results show a definite overall improvement in symptoms following enterocystoplasty.

Table 4 Symptomatic Post-operative Results

	"Cured"	*Better*	*Same*	*Worse*
Frequency and nocturia	6	5	0	4
Enuresis	4	2	1	0
Bladder pain	4	0	1	0
Urgency/incontinence	4	1	0	2

Post-operative tests showed normal haemoglobin, urea and electrolytes in all patients. Six patients had urinary infection diagnosed but because of the enterocystoplasty it was difficult to differentiate bowel organisms from true urinary pathogens.

Some of these patients, particularly those with irritable bladder syndrome, had had many years of medical investigation and treatment, and with the general improvement following enterocystoplasty they were unwilling to undertake more invasive investigations. Thus, only 3 patients agreed to follow-up excretion urography and only 2 attended for cystoscopy. These investigations revealed normal upper tracts and confirmed the increased capacity of the bladder.

Table 5 Pre-operative and Post-operative Urine Flow Rate and Sphincterometry

	Flow rate (ml/sec)		*Maximum Urethral Closure Pressure (cm H_2O)*	
Patient	pre-op	post-op	pre-op	post-op
H.E.	7*	10*	140	120
E.A.	24	40	38	48
B.W.	4	7	120	104
A.Y.	17	19	108	116
G.P.	35	25	130	128
S.L.	20	5*	120	136

*volumes too small for acurate measurement

Urodynamic Studies

Flow rate There was no significant change as a result of the operation, mean flow rate being 17.8 ml/sec both before and after surgery (Table 5).

Sphincterometry No significant alteration was seen in maximum urethral closure pressure. Mean pre-operative and post-operative values were 109.3 cm H_2O and 108.6 cm H_2O respectively. It was noted that 5 patients had sphincter pressures considerably above the normal range (Table 5).

Detrusor stability Four patients, all with irritable bladder syndrome, were initially unstable and remained so after enterocystoplasty. Similarly, the 2 patients with interstitial cystitis both had stable bladders which did not change post-operatively.

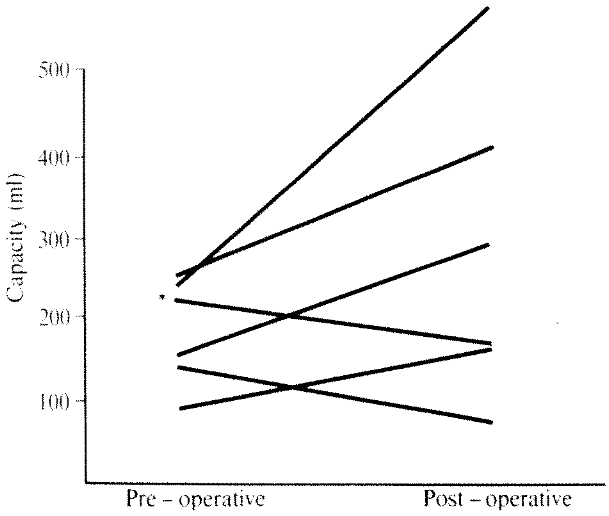
One patient had undergone prolonged bladder distension 4 weeks prior to enterocystoplasty and hence has been excluded from the results in the next 4 observations.

First desire to micturate The bladder capacity at first desire to micturate was increased in 4 of the 5 patients studied. However, it was no longer followed by intense urgency as in the pre-operative examination.

Voiding pressure Intrinsic detrusor voiding pressure was reduced dramatically in all 5 patients from a mean of 133 cm H_2O to a post-operative mean of 50 cm H_2O.

Residual urine This was present in only 1 patient pre-operatively but subsequently noted in 4 patients following enterocystoplasty (range 30 – 230 ml.)

Capacity In 4 of 5 cases the bladder capacity was increased by a significant margin (Fig.).



*4 weeks post – distension

Fig. Pre-operative and post-operative bladder capacity.

Complications

Complications were frequent and some potentially serious. Four patients developed urinary fistulae, all of which closed spontaneously. Pelvic sepsis developed in 10 patients. Thrombosis of the pelvic venous plexus occurred in 2 patients – a serious complication in view of the young age of the patients – however, both recovered fully without pulmonary complications. Six patients developed urinary tract infections.

There was one incident of secondary haemorrhage and 1 patient developed acute urinary retention, which settled after a period of catheter drainage. Mucous discharge was noted in the urine of all patients following operation but caused no problems.

Discussion

The patients with malignant disease in this series would now be treated by other means. In recent years enterocystoplasty has been used primarily for intractable cases of both irritable bladder syndrome and interstitial cystitis in which prolonged distension therapy has failed to relieve symptoms. It should be emphasised again that these are patients who have severe symptoms extending over many years, and who have undergone extensive investigation and treatment prior to surgery.

The subjective symptomatic improvement described by these patients corresponded to the objective results obtained with urodynamic studies on the limited number of patients in whom this was possible. The increase in capacity and the marked decrease in voiding pressures demonstrated urodynamically would be expected to lead to an improvement in the symptoms of frequency and urgency.

The increase in capacity could also be responsible for the improvement in the enuretic patients. Although no patient has become totally dry, the majority were dramatically improved. The pain associated with interstitial cystitis, though not completely abolished by the operation, occurs at a higher bladder capacity, effectively alleviating the patient's symptoms.

Increase in residual urine is well described after enterocystoplasty. Micturition is rendered inefficient (Gleason *et al.*, 1972) and urine is expelled into the iatrogenic diverticulum which is effectively non-contractile. Intra-abdominal straining during voiding may empty the diverticulum and the bladder completely but this was possible in only one of our 4 patients who had post-operative residual urine. Selective sphincterometry has been advocated (Turner-Warwick and Ashken, 1967) to redress the balance of micturition but this treatment must be open to question in patients with unstable bladders.

We have at present accepted the presence of residual urine as a necessary side effect of enterocystoplasty in this group and it would seem to us to be an acceptable price to pay for a degree of symptomatic relief in these patients. So far no patient has developed a chronic urinary infection and long-term problems related to the diverticulum and residual urine are not yet apparent.

Nonetheless, improvement in symptoms after enterocystoplasty is sufficiently encouraging to make this operation worthy of consideration in cases of irritable bladder syndrome and interstitial cystitis with severe symptoms in which all other recognised treatment has failed.

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Idiopathic Bladder Instability Treated by Biofeedback

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Summary—Biofeedback training has been used to treat 27 female patients suffering from symptoms associated with detrusor instability Re-education to auditory and visual stimuli took place during 4 to 8 one-hour sessions at weekly intervals. Using subjective and objective methods of assessment 81% of the patients were improved following treatment.

Detrusor instability is the most common cause of the symptoms of urgency, urge incontinence and frequency of micturition, and is extremely difficult to treat. Idiopathic detrusor instability may be due to a failure of cortical inhibition in which emotional factors play a dominant role (Frewen, 1972).

Biofeedback training is a form of learning or re-education in which the patient is placed in a closed feedback loop where one or more of her normally unconscious physiological processes is made available to her as a visual, auditory or tactile signal (Stroebel and Glueck, 1973). It has been used to treat other disorders of autonomic function including hypertension, migraine and long-standing faecal incontinence with moderate degrees of success (Engel *et al.*, 1974; Love *et al.*, 1974; Sargent *et al.*, 1973).

In this study we have used biofeedback to treat women with detrusor instability whose symptoms varied in severity, all of whom had failed to respond to other methods of treatment.

Patients and Method

Thirty-two female patients entered and 27 completed the study. They have been followed up for a minimum of 3 months (range 3 to 15 months). Their average age was 41 years (range 18 to 64 years) and they were given an average of 5.4 sessions of treatment.

The detailed methodology has already been described (Cardozo *et al.*, 1978). Detrusor instability was diagnosed by cystometry or videocystourethrography with pressure and flow studies, if a pressure rise greater than 15 cm of water occurred during bladder filling or provocative testing. Neurological abnormalities, outflow obstruction and organic bladder pathology were excluded by physical examination, cystometry, cystoscopy and uroflowmetry.

Biofeedback training took place during 4 to 8 one-hour sessions, when the detrusor pressure was measured by means of cystometry and converted into auditory and visual stimuli, thus making the patient aware of the changes in bladder pressure. If after 4 sessions at weekly intervals there was no significant improvement, therapy was stopped; otherwise it was continued until cystometry was normal, up to a maximum of 8 sessions. Between sessions patients kept a urinary diary which was used as a measure of their symptomatic improvement. At the end of treatment a further cystometrogram was performed to assess objective improvement.

Patients were considered to be subjectively cured if they no longer complained of frequency, urgency or urge incontinence, and objectively cured if they no longer exhibited detrusor contractions, or a pressure rise greater than 15 cm of water, or leakage of urine at any time during cystometry.

Results

The results are shown in Table 1. Five patients, all of whom had severe detrusor instability, with detrusor contractions greater than 60 cm of water and capacities less than 200 ml, completely failed to respond to biofeedback treatment. One of them was later found to be suffering from multiple sclerosis. Two of the 5 enuretic patients stopped bedwetting altogether, 2 were greatly

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Table 1 Results for the 27 Patients

	Subjective	*Objective*
Cured	11	12
Improved	11	4
Failed	5	11

improved and the other one was unchanged. The detailed symptomatic changes are shown in Table 2. Frequency was greatly improved and fell from a diurnal mean of 11.7 times and a nocturnal mean of 2.1 times to 6.8 and 0.8 respectively.

The cystometric changes are shown in Table 3. The actual reduction in the total maximum pressure rise was from 57 to 43 cm of water; however, if the 11 patients who failed objectively are excluded the figure drops to 22 cm of water.

No urinary tract infections were encountered. Eleven patients who were cured both subjectively and objectively remained symptom-free 3 months after treatment. Four of them had been followed up for over 1 year and are still asymptomatic.

Discussion

The results of biofeedback can be compared to the improvement produced by other forms of treatment in detrusor instability. Surgery originally aimed at denervating the bladder and in one series Ingleman-Sundberg (1959) claimed a cure or improvement in 25 out of 32 patients, but the improvement did not last. Sacral neurectomy is successful only in carefully selected cases. Out of 9 patients treated in this way Torrens and Griffiths (1974) cured 2 and improved 5. Cystodistension is in current use, and Ramsden *et al.* (1976) reported a series of 51 cases out of which 11 were cured and 25 improved, but the long-term results are poor, and other series have not produced these results.

Table 2 Subjective Changes for the 27 Patients

Symptoms (No. of patients)	*Before*	*After*
Frequency, Diurnal	23	10
Nocturnal	18	5
Urgency, Total	26	17
Severe	25	9
Urge incontinence, Total	22	15
Severe	20	4
Enuresis	5	3

Table 3 Objective Changes for the 27 Patients

VCU/CMG (mean)	*Before*	*After*
First sensation (ml)	145	214
Capacity (ml)	374	446
Pressure rise on filling (cm H_2O)	40	34
Total maximum pressure rise (cm H_2O)	57	43
Detrusor contractions (No. of patients)	26	14
Leaks (No. of patients)	25	12

Bladder drill with supportive psychotherapy is being tried by Frewen (1978) and the results seem promising. He quotes a cure rate of 80%. However, satisfactory treatment often requires the patient to be admitted to hospital for 10 days. Drug therapy is still the most widely used form of treatment and various studies estimate that beta-adrenergic stimulators and anticholinergic preparations help 50 to 80% of patients (Brown *et al.*, 1973; Stanton, 1973).

Biofeedback avoids the morbidity of surgery and the side effects of drugs. In patients with mild to moderate detrusor instability it may produce a complete cure. Biofeedback also helps by giving patients a better understanding of bladder function and of their particular bladder problem. However, it is extremely time-consuming, requiring up to 8 h of treatment administered by a doctor or highly trained nurse and technician. Failure to attend sessions amounted to about 15% and 5 (16%) of the initial group did not complete their treatment, 2 because of the time involved, 2 because they felt the treatment was not helpful and one did not like being catheterised each week. For patients to do well with this form of treatment they need to be highly motivated and reasonably intelligent; otherwise they are unable to associate the auditory and visual stimuli with their symptoms. Biofeedback is not helpful in severe detrusor instability, when the first sensation of desire to void and a large detrusor contraction occur simultaneously. This is because the patient does not have enough time to inhibit the contraction before it occurs.

Patient selection could be employed to improve the results of biofeedback training. In a pilot study using the Middlesex Hospital questionnaire, on 15 of the patients treated it was found that the mean directional hostility score for those who failed (6 patients) was 11.83, whereas for those who were improved or cured (9 patients) the mean was 4.56. It is interesting to note that the mean directional hostility score for the whole group was 6.64, which is extremely high, the normal being taken as 0.5.

Our results show 81% of a group of 27 patients with idiopathic detrusor instability have been helped by biofeedback training, and that the improvement is lasting. We feel this is sufficient for it to warrant consideration as a method of treatment for the unstable bladder.

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Bladder Instability in Women with Recurrent Cystitis

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Summary—Factors in the aetiology of bladder instability in women with recurrent cystitis are analysed. A multifactorial approach to patient management is advocated and supported by a treatment failure rate of only 3.6% with these patients over a mean follow-up of nearly 2 years.

The recognition of bladder instability (the finding of uninhibited detrusor contractions during filling cystometry) in different groups of patients over the last 10 years has posed many questions.

Detrusor instability is physiological in the very young and associated with nocturnal enuresis in schoolchildren. It is of clinical significance in the neuropathic bladder of spinal trauma or multiple sclerosis, and recognised as a cause of failure in the surgery of incontinence in women (Hodgkinson, 1965). Instability is a common finding in men with benign prostatic hypertrophy in whom it is usually reversed by surgery (Turner-Warwick *et al.*, 1973).

The significance of detrusor instability in women presenting with recurrent attacks of dysuria and increased frequency, including lower urinary tract infection and the "urethral syndrome" (and here collectively called recurrent cystitis), was reported by Lapides and Costello in 1969. They found an incidence of 16% in women with documented urinary tract infection and related susceptibility to infection to relative ischaemia of the bladder wall secondary to high detrusor resting and voiding pressures. A more detailed urodynamic analysis by Rees *et al.* (1976) revealed an incidence of 27% in women with recurrent cystitis and showed that bladder outlet obstruction in these patients is rare. It was also found that trabeculation tended to be associated with instability and not with obstructed micturition.

It has also been reported (Rees and Farhoumand, 1977) that patients with bladder instability have a characteristic psychometric profile using the standardised Middlesex Hospital Questionnaire, Eysenck Personality Questionnaire and Salkind's Morbid Anxiety Inventory. Compared with age and sex matched normal controls, patients with bladder instability are particularly anxious, have high scores for psychoticism or tough-mindedness, and are more prone to somatic manifestations of anxiety than any other group. The latter is most marked in younger patients with bladder instability compared with normal matched controls ($P<0.001$). Conversely these patients are significantly less obsessive and depressed than other groups except normals.

Farrar *et al.* (1976), in a study of women with outlet obstruction, observed that those who had bladder instability (46%) were twice as difficult to render asymptomatic as those with stable bladders. Dunn *et al.* (1974) advocated the use of prolonged bladder distension in the treatment of urgency and urge incontinence due to detrusor instability. Torrens and Griffith (1974) have used sacral neurectomy.

In the absence of overt neurological disease the cause of bladder instability in most women is not known. This study has looked at a large number of factors that might be relevant and reports the results of treatment based on a multifactorial approach to women with recurrent cystitis.

Patients and Methods

During a 2-year period (1974-1976), 242 women with recurrent attacks of dysuria and increased frequency of micturition were referred to the Urinary Infection Clinic at the Institute of Urology, London. Fifteen women were excluded from the study by the finding of abnormalities on intravenous urography that led to major surgery or other treatment inappropriate to a urinary infection clinic. Eighteen patients were unable or unwilling to be admitted to hospital for investigation. There remained 209 women

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who have been fully assessed by methods previously described (Rees *et al.*, 1976; Rees and Farhoumand, 1977).

Most patients had additional symptoms associated with attacks of frequency/dysuria and many had lesser symptoms between attacks. In order to assess the possibility of making a *clinical* diagnosis of instability, the incidence of reported symptoms was compared for patients with stable and unstable detrusors with particular reference to whether additional symptoms were associated only with attacks, or continued to a lesser extent between attacks. The intermittent and/or continuous symptoms analysed were urgency, urge incontinence, nocturia, hesitancy, a feeling of incomplete emptying, restricted urinary stream, haematuria, suprapubic pain or discomfort, loin pain, lumbar spinal pain, dyspareunia and vulvovaginitis.

Cystometry was performed with the patient seated on a modified commode. Saline at room temperature was instilled via a urethral catheter at 150 ml/min. Detrusor pressure was recorded using automatic subtraction of rectal pressure with cough and change of posture provocation. Other routine urodynamic measurements were obtained including residual urine, bladder capacity, detrusor pre-micturition and maximum voiding pressures, urine flow rate, urethral calibre and urethral closure pressure. Bacteriuria was defined as the finding of at least 10^8 organisms per litre in a fresh clean catch midstream or cystoscopy specimen of urine, at any time during the period of follow-up. The observation of trabeculation was made only when it was unequivocal with the bladder filled to capacity at cystoscopy (performed in all cases).

Routine management included maintenance of an above average fluid intake, care with vulval and sexual hygiene, regular voiding, appropriate antibiotic therapy for proven urinary tract infection, treatment of associated vaginal infection, oestrogen replacement where necessary, psychiatric counselling and supportive psychotherapy for sexual and psychological disturbances and surgical treatment of urological and gynaecological abnormalities.

Of the 55 patients with bladder instability, 33 remained symptomatic after initial assessment and treatment. These were then given full standard doses of the drugs shown in Table 1. A switch from emepronium to flavoxate or vice versa was made in patients who failed to respond to the drug of first choice. In 10 patients with persistent symptoms imipramine was added cautiously to minimise the side effects that such drug combinations sometimes produce.

Table 1 Drug Therapy in Patients with Detrusor Instability

Emepronium (Cetiprin) 200 mg	20
Flavoxate (Urispas) 200 mg	4
Emepronium Changed to Flavoxate	7
Flavoxate Changed to Emopronium	1
Propantheline 30 mg (given 3 times a day)	1
Imipramine (Tofranil) 25 to 75 mg (given at night)	10

Urethral dilatation to between 34 and 40 FG (mean 37.5 ± 2.27) was performed in 17 patients and internal urethrotomy (using the Otis instrument) at between 30 and 45 FG (mean 37.0±3.9) in a further 9. The indications are summarised in Table 2.

Results

Incidence

Uninhibited detrusor contractions were recorded in 55 patients (26.3%). A further 36 (17.2%) had

Table 2 Indications for Urethral Dilation and Internal Urethrotomy in Patients with Detrusor Instability (n = 55)

	Defined as	*Dilatation*	*Urethrotomy*
Outlet obstruction	Urethral calibre< 19 FG peak flow rate< 11 ml/s despite adequate max. voiding pressure> 20 cm H_2O	4	2
Outlet inhibition	Peak flow rate< 11 ml/s despite adequate urethral calibre> 20 FG and max. voiding pressure> 20 cm H_2O	4	2
Reduced urethral calibre	< 19 FG	1	1
Reduced peak flow rate	< 11 ml/s	3	0
Increased max. urethral closure pressure	> 100 cm H_2O	1	4
Empirical	Previous relief of symptoms	4	0
	Totals	17	9

detrusor pre-micturition pressures of 15 cm of water or more, but were stable. The remaining 118 (56.5%) had normal filling cystometry. Bacteriuria was established in only 34% of all cases during a mean follow-up of 2 years, and the incidence was the same for stable and unstable bladders (Table 3).

Age

The figure shows the age distribution of the patients with detrusor instability. The proportion dropped with successive decades, although the percentage of stable bladders with high pre-micturition pressures remained fairly constant with age. There was no difference in the length of history between those with stable and those with unstable bladders.

Symptom Analysis

Continuously increased frequency of micturition ($\chi^2 = 4.04$, $P<0.05$) and loin pain ($\chi^2 = 4.27$, $P<0.05$) were the only 2 symptoms to have a statistically significant association with detrusor instability in these patients with recurrent cystitis. A relationship between bladder trabeculation and instability has been noted previously ($\chi^2 = 3.84$, $P<0.05$). In this study a more significant association has been found between trabeculation and a pre-micturition detrusor pressure in excess of 14 cm of water (Table 4).

Hormonal Factors

Detrusor instability was uncommon in women found to have atrophic vulvitis ($\chi^2 = 7.39$, $P<0.01$). These patients were almost all over 45 years old and, as has been shown, the incidence of instability dropped to 12.5% in this age group. Conversely, women on oral contraception were more likely to have unstable bladders than others, but the difference was not statistically significant.

Table 3 The Incidence of Bacteriuria in Stable and Unstable Bladders

	Abacteriuric	*Bacteriuric*	*Total*
Stable	101	53	154
Unstable	37	18	55
	138	71	209
% Unstable	26.8	25.4	26.3

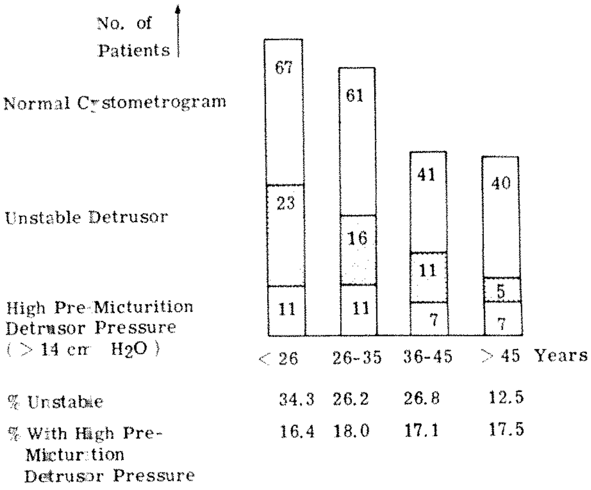

Fig. Relationship between detrusor instability and age.

Other factors

These include the relationship to menstruation, parity, previous pelvic surgery, and hygiene (including regularity of bathing, washing and douching, the use of vaginal aerosol deodorants, bath salts and oils) and were not related to bladder instability. Physical findings such as cervical erosion, chronic cervicitis, cystocele, obesity, haemorrhoids and vaginal infection with monilia, *Trichomonas* or *Corynebacterium* (*Haemophilus*) *vaginalis* likewise provided no significant relationship with bladder instability.

Drug Therapy

Drugs such as emepronium and flavoxate sometimes supplemented by imipramine were found to be useful for symptomatic relief. Emepronium had to be withdrawn in one patient because of severe nausea and vomiting and in another be-

Table 4 The Relationship between Trabeculation and Elevated Pre-Micturition Pressure

	Pre-Micturition Detrusor Pressure		*Total*
	< 15 cm H_2O	*15 cm H_2O or more*	
Trabeculation	11	18	29
No Trabeculation	107	54	161
	118	72	190

(Excluding 19 Unstable Bladders with Pre-Micturition Pressures below 15 cm H_2O)

$\chi^2 = 8.5$ $P<0.005$

cause of marked fluid retention (not urinary retention). A controlled trial of these drugs has not been undertaken in this study because a multifactorial management concept makes a valid comparison impossible. There was little to choose between emepronium and flavoxate overall: one suited some patients better than the other, justifying a switch in medication.

Results of treatment

These are summarised in Table 5. All of these patients were referrals from general practice or from other hospitals, in whom previous treatment had failed. Symptoms were a little more difficult to abolish in patients with detrusor instability, but the overall management failure rate is the same for patients with stable and unstable bladders at between 3 and 4%.

Discussion

The significance of demonstrating detrusor instability in more than a quarter of these patients is unclear as the incidence of this finding in normal women is not known. The reducing incidence with age suggests that delayed maturation of cortical inhibition of detrusor function may be a factor in the aetiology of adult detrusor instability. The percentage of women with high pressure bladders, however, stays constant with age. Apart from this difference the 2 groups of patients (unstable detrusors and high pressure detrusors) were remarkably similar in symptomatology, physical findings and psychometric profiles.

Symptoms were a poor guide in making a diagnosis of bladder instability in these patients, as the classical symptoms of instability occurred in the majority of patients presenting with recurrent cystitis. The association of loin pain with instability may perhaps be explained by an occult neuropathic element. Only one patient (mild congenital hemiparesis) had peripheral neurological signs. It has been shown that the common symptom of loin pain cannot be attributed to renal abnormality or urinary infection in the majority of women presenting with recurrent cystitis (Rees, 1978). Loin and lumbar spinal pain disappeared in 9 out of 10 patients established on regular lumbar spinal exercises, suggesting that these symptoms are usually musculoskeletal in origin.

Table 5 Follow-up of Patients Referred to Urinary Infection Clinic (209)

	All Patients	*Detrusor Instability*
Cured-Asymptomatic and Abacteriuric	75.6%	70.9%
Minimal symptoms	10.6%	16.4%
Improved (and not sought further medical help)	10.6%	9.1%
Minimal improvement and no change = management failure	3.2%	3.6%

Mean follow-up 21.4 months ± 4.3

In this study there was no evidence to support the popular belief that in some cases bladder instability might be secondary to recurrent urinary tract infection. The finding of trabeculated bladders in women with recurrent cystitis suggested a high pressure bladder (including instability) but not necessarily outlet obstruction—an uncommon finding (7%) in these patients. Trabeculation is assumed to result from high pressure or uncoordinated detrusor activity, whereas pure obstruction would be expected to produce a uniform smooth muscle hypertrophy. Outlet obstruction is common in older men, amongst whom many have bladder trabeculation and the majority have detrusor instability (Turner-Warwick *et al.*, 1973).

That hormonal influences may play a part in the aetiology of bladder instability is suggested by the inverse relationship with atrophic vulvitis, and the increased incidence in patients on oral contraception with oestrogen/progestogen preparations.

Patients with detrusor instability have a characteristic psychological make-up, helping to confirm a strong clinical impression that these patients are helped by supportive psychotherapy. Controlled trials are necessary to establish the efficacy of tricyclic (*e.g.* imipramine) and other antidepressants in adult detrusor instability. That they are of use in nocturnal enuresis was shown as long ago as 1964 by Hagglund and Parkkulainen. Khanna *et al.* (1975) suggest that the mode of action in the canine lower urinary tract is the stimulation of alpha adrenergic receptors in the bladder neck and urethra. They also have anticholinergic properties as well as their central nervous system effects.

It is concluded that a multifactorial approach to the management of any patient with recurrent cystitis is well worthwhile. The low treatment failure rate in this study indicates that procedures such as prolonged bladder distension, bladder denervation and selective sacral neurectomy should be considered only very rarely in patients with recurrent cystitis who have detrusor instability.

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Bladder Rupture: An Acceptable Complication of Distension Therapy?

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Summary—Bladder rupture complicating prolonged bladder distension is reviewed. Rupture occurred in 7 of 128 distensions for detrusor instability, in 5 of 34 distensions for interstitial cystitis and in one of 4 distensions for reduced bladder capacity of unknown aetiology.

Management of extraperitoneal ruptures should be conservative. Intraperitoneal ruptures should probably be explored.

Rupture was more likely if the bladder wall was diseased, the distension pressure exceeded 145 cm H_2O, and the patient was more than 50 years old.

The eventual outcome of prolonged bladder distension was not adversely affected by bladder rupture.

Prolonged bladder distension under epidural anaesthesia was introduced by Helmstein for the treatment of bladder carcinoma. In Oxford the technique has been modified and used in the treatment of detrusor instability (Dunn *et al.*, 1974; Ramsden *et al.*, 1976) and interstitial cystitis (Dunn *et al.*, 1977). This type of distension remains our treatment of choice in these conditions in severely affected patients, in whom conventional therapy has failed and in many of whom the only alternative treatment would be a urinary diversion. It has also been used for treating a small number of patients with reduced bladder capacity of unknown aetiology.

Complications of the procedure have included haematuria, backache and urinary retention but these have been of short duration. Bladder rupture has also occurred and has been mentioned in previous communications (Ramsden *et al.*, 1976; Dunn *et al.*, 1977). The purpose of this paper is to describe our experience with this complication of therapy in more detail and discuss its diagnosis, management, possible aetiological factors and effect on the outcome of distension.

Patients and Methods

One hundred and sixty-seven prolonged bladder distensions have been performed on 113 patients with detrusor instability, interstitial cystitis, reduced bladder capacity of unknown aetiology and post-irradiation bladder fibrosis. The bladder was ruptured during the distension in 13 patients (*i.e.* 8% of distensions). In no patient was the bladder ruptured on more than one occasion (Table 1).

Diagnosis of Bladder Rupture

The bladder may rupture during distension (a) alone or (b) together with the distension balloon. The clinical features of each situation are shown below:

(a) Bladder Rupture with Intact Distension Ballon (6 Patients)

(i) Continuous rapid emptying of the infusion. chamber and a large infusion volume (> 1300 ml).
(ii) Post-distension abdominal pain.
(iii) Post-distension retention of urine.

(b) Rupture of both the Bladder and the Distension Balloon (7 Patients)

(i) Continuous rapid emptying of the infusion chamber and a large infusion volume (> 1300 ml).
(ii) The signs of shock or the vasovagal syndrome during distension.
(iii) Loss of the palpable "bladder".
(iv) Suprapubic coldness and bogginess.
(v) Blood stained and incomplete bladder drainage. (N.B. This will also be present if the balloon alone ruptures.)

When both the bladder and the balloon burst the clinical picture is dramatic and the diagnosis

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Table 1 The Incidence of Bladder Rupture in each Diagnostic Category of Patients undergoing prolonged Bladder Distension

Diagnosis	*No. of patients*	*No. of prolonged bladder distensions*	*No. of bladder ruptures*	*Bladder rupture (%)*
Detrusor instability	93	128	7	5
Male	30	36	1	3
Female	63	92	6	7
Interstitial cystitis	15	34	5	15
Male	6	13	2	15
Female	9	21	3	14
Small bladder capacity				
Aetiology unknown	4	4	1	25
Post-irradiation	1	1	0	–

obvious but when the bladder alone bursts the diagnosis may be missed until the epidural anaesthetic has worn off and the overnight catheter has been removed.

Diagnosis was confirmed by cystography (Fig. 1). This helped to distinguish between intraperitoneal and extraperitoneal rupture. Twelve of the 13 ruptures were extraperitoneal, with a tendency for the contrast medium to be extravasated to the right.

Cystoscopy may also be performed but may be confusing because of bleeding. The tear, if seen, is usually crescentic in shape and on the posterior/superior aspect of the bladder.

Treatment

It is our policy to manage these patients conservatively with free catheter drainage until the leak has been shown to be healed on cystography. The first cystogram is performed after one week and thereafter at weekly intervals if necessary.

All patients are given a broad spectrum antibiotic and regular urine cultures are made during the period of catheter drainage. Three patients developed infected urine (Case 3—*Proteus mirabilis*, Case 6—*E. coli* and Case 10—*Staph. aureus*), but responded satisfactorily to a change to the appropriate antibiotic.

Catheter drainage was necessary for 3 to 16 days (mean 12.2 ± 1.3 days) in the 12 cases with extraperitoneal rupture, but for 49 days in the patient with an intraperitoneal rupture.

Patients were discharged home the day after catheter removal if satisfactory voiding was established. One female patient required repeated catheterisation and eventually internal urethrotomy to establish normal micturition.

Prognosis

Follow-up has been possible in all cases, from

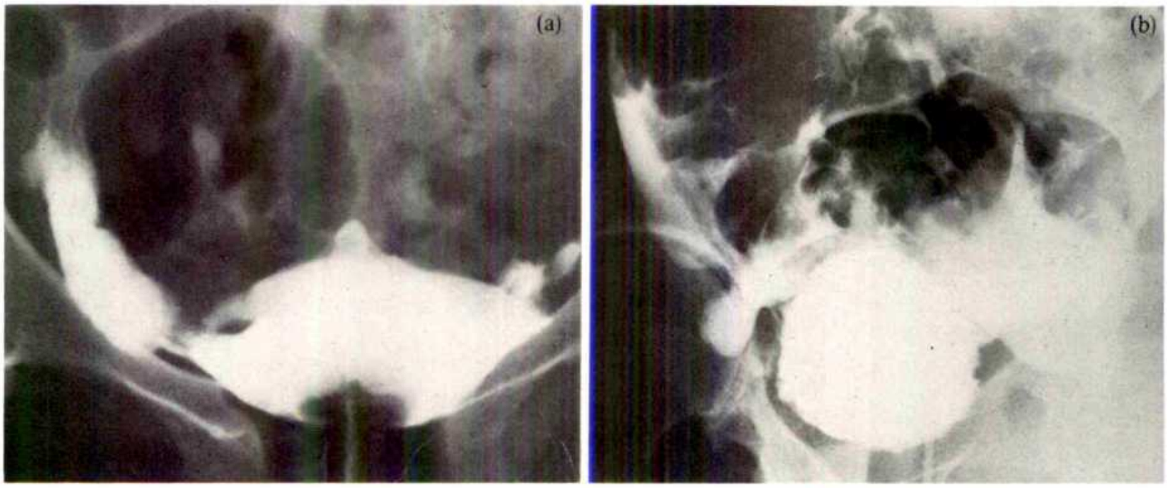

Fig. 1 Cystograms of (a) Patient 12 showing extraperitoneal bladder rupture and (b) Patient 10 showing intraperitoneal rupture.

Table 2 Prognosis following Bladder Rupture during Prolonged Bladder Distension

Patient	*Diagnosis*	*Follow-up period (months)*	*Result*
1	Unstable	7	Improved
2	Unstable	9	Improved
3	Unstable	3	Unchanged
4	Interstitial cystitis	24	Improved for 18/12, underwent 2nd PBD and improved at 6/12 following this.
5	Interstitial cystitis	6	Improved but symptoms slowly returning.
6	Interstitial cystitis	15	Improved
7	Interstitial cystitis	6	Improved but frequency returning.
8	Unstable	3	Improved
9	Unstable	3	Symptom-free for 1/12, then complete relapse of symptoms
10	Unstable	1	Unchanged
11	Interstitial cystitis	1	Improved
12	Unstable	3	Improved
13	Small capacity bladder	1	Worse

(Unstable = detrusor instability)

one month to 2 years after rupture (Table 2). Five of the patients with detrusor instability were improved but one relapsed after only one month, having been entirely symptom-free for that period. Two patients remained unchanged. The patients with interstitial cystitis did well. All were improved, and in 4 the improvement lasted for 6 months or more. Bladder rupture appears to be particularly effective in relieving their pain and when relapse of symptoms occurs, it is frequency which then predominates. Only one patient has been made worse. She had a prolonged bladder distension for symptoms suggestive of interstitial cystitis but had a normal bladder on cystoscopy.

Factors Leading to Bladder Rupture

The factors which lead to bladder rupture in a particular patient during prolonged bladder distension are not clear. It is perhaps surprising that bladder rupture does not occur in more patients during this treatment (Table 3).

(a) Factors Related to the Technique of Bladder Distension

(i) Maximum distension pressure

This varied from 80 to 156 cm H_2O (mean 140±6.5 cm) and compares with a mean of 133.6±2.4 cm in those patients whose bladders did not rupture. In 7 of the 13 ruptured patients

Table 3 Details of possible Aetiological Factors in each patient with Bladder Rupture during Prolonged Bladder Distension

Patient	*Sex*	*Age*	*Diagnosis*	*Maximum distension pressure (cm H_2O)*	*Distension duration (h)*
1	Female	51	Unstable	125	2
2	Female	48	Unstable	80	2
3	Female	83	Unstable	?	½
4	Female	65	Interstitial cystitis	155	2
5	Female	71	Interstitial cystitis	120	1
6	Female	44	Interstitial cystitis	150	1
7	Male	50	Interstitial cystitis	150	1
8	Female	58	Unstable	150	3
9	Female	30	Unstable	145	1
10	Male	29	Unstable	156	1½
11	Male	41	Interstitial cystitis	145	¼
12	Female	66	Unstable	130	½
13	Female	67	Small capacity bladder	112	1½

(Unstable = detrusor instability)

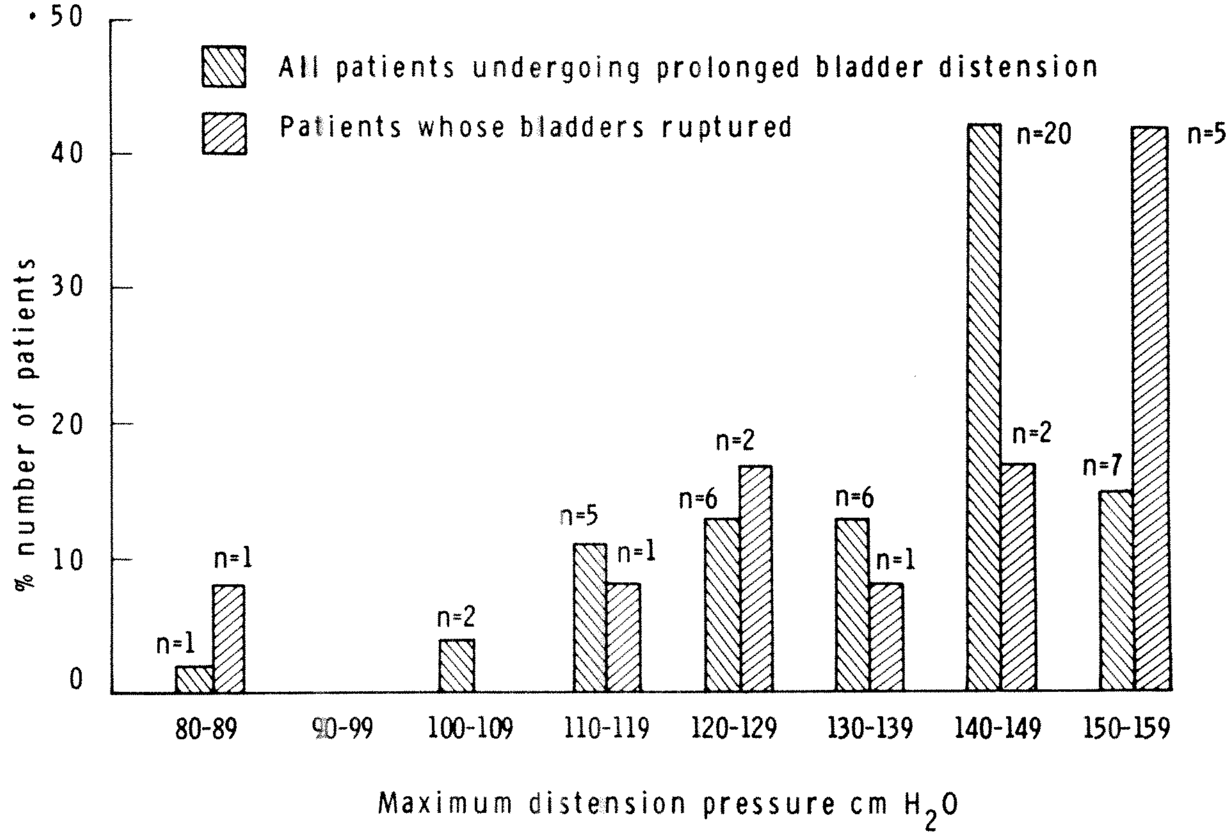

Fig. 2 The maximum distension pressure used in a series of 47 consecutive patients undergoing prolonged bladder distension and 13 patients whose bladders ruptured.

the distension pressure exceeded 145 cm H_2O and in 5 the pressure was 150 cm or more. The proportion of patients subjected to this higher pressure was greater in the group that ruptured than in an unselected group of 47 whose bladders remained intact (Fig. 2).

(ii) The duration of distension
Rupture occurred as early as 15 min and after as long as 3 h (Fig. 3). In 10 patients the bladder ruptured after distension had been in progress for more than one hour.

(b) Patient Factors

(i) Bladder wall disease
Bladder rupture was more common in patients with interstitial cystitis (and therefore with presumed bladder wall disease) than in those with detrusor instability ($\chi^2 = 2.13$, $P < 0.005$ on Fisher's Exact Test). Previous bladder rupture and consequent bladder scarring does not appear to predispose to further rupture as 2 patients have subsequently had uncomplicated bladder distensions.

(ii) Sex of patient
Rupture occurred in 10 female and 3 male patients. This sex distribution closely mirrors that of the whole series of prolonged bladder distensions (118 female:49 male).

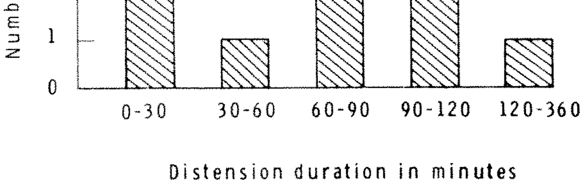

Fig. 3 The time at which bladder rupture occurred during prolonged bladder distension in 13 patients.

(iii) Age of patient

The mean age of the patients whose bladders ruptured (53 ± 4.5 years) was not significantly greater than that of patients whose bladders did not rupture (41 ± 1.9 years). Eight of the 13 cases with bladder rupture were, however, more than 50 years old, and a comparison with an unselected group of patients undergoing prolonged bladder distension shows that a higher proportion of these patients are in the older age groups (Fig. 4).

(iv) Bladder biopsy before distension

This was performed in one patient early in the series, and although most biopsies are superficial, it is now our policy to wait 3 to 4 weeks before performing distension.

(v) Detrusor contraction during distension

In 3 cases bladder sensation returned shortly before bladder rupture. It is therefore possible that bladder motor activity had also returned at this time and that detrusor contractions had contributed to the process of rupture.

Discussion

Rupture of the normal bladder following trauma is well documented. Spontaneous cases of rupture have also been recorded (Bastable *et al.*, 1959; Bliss *et al.*, 1964; Wheeler, 1972) but in these cases there is almost invariably bladder overdistension in the presence of an associated predisposing factor, *e.g.* tuberculosis or carcinoma. Both Coombes (1975) and Helmstein (1972) observed bladder rupture during distension therapy for carcinoma and the higher incidence of rupture in the interstitial cystitis group in our series emphasises that bladder wall disease is an important factor in pathogenesis. The site of rupture, as in our cases, was in the vault or at the junction of the posterior and superior walls of the bladder. This is said to be the weakest part of the bladder, being covered only with peritoneum and without fascial or bony protection and is the site at which the bladder ruptures experimentally in the cadaver.

The mortality rate in some of the older series of bladder rupture is high. Bastable *et al.* in 1959

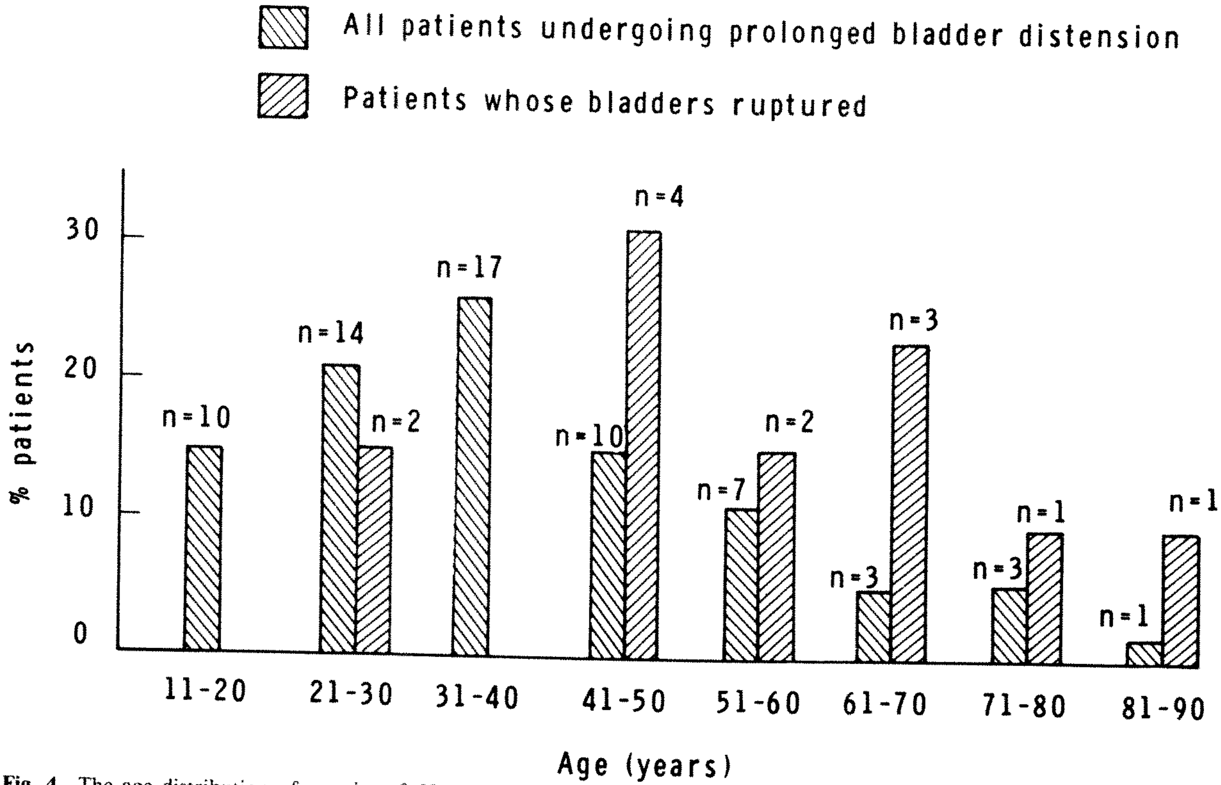

Fig. 4 The age distribution of a series of 65 consecutive patients undergoing prolonged bladder distension and 13 patients whose bladders were ruptured.

reported a mortality of 47%, Stone (1931) having reported 46%. Death in these series was attributed to the underlying disease, haemorrhage, or infection of the extravasated urine and consequently an aggressive approach was adopted in management. Extravasated sterile urine, however, is probably rapidly absorbed and therefore poses no threat (Mitchell, 1971), provided that the appropriate antibiotic prophylaxis is given against infection and recently a more conservative approach has been suggested in the treatment of, in particular, extraperitoneal bladder rupture. We have no cause to regret the conservative approach adopted in the 12 patients in whom the rupture was extraperitoneal and can see no benefit to be gained from exploration and suture of the bladder with drainage of the extravasated fluid. The bladder healed satisfactorily in all of these cases, within an acceptable time and with a low morbidity. The patient in whom the rupture was intraperitoneal required a much longer period of catheter drainage and it is possible that more rapid bladder healing would have been achieved by operative repair of the defect, although Robards *et al.* (1976) successfully managed cases of traumatic intraperitoneal bladder rupture with catheter drainage alone.

Rupture of the bladder does not adversely affect the outcome of prolonged distension for either detrusor instability or interstitial cystitis; indeed the quality of improvement appears to be enhanced, especially in the group with interstitial cystitis. We believe that prolonged distension of the bladder may result in ischaemic nerve damage. Rupture of the bladder may also result in physical disruption of the parasympathetic detrusor nerve supply and hence be more effective than distension alone.

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A New Self-Retaining Catheter with Triple Microtip Pressure Transducer: "The Baghdad Modification"

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Summary—A new self-retaining triple microtip pressure transducer on a silicone rubber catheter was assessed on 12 patients with bladder neck obstruction or obstruction at the distal urethral component (external sphincter). The catheter gave reliable and accurate information on pressures in the bladder, prostatic and bulbar urethras simultaneously. It is, however, an expensive piece of equipment and requires delicate handling.

Reliable measurement of the bladder and urethral pressure is of great importance in the diagnosis and treatment of many urological disorders. Several methods are currently employed and the majority are based on the use of an open-ended catheter connected to an external pressure transducer such as the instrument designed by Brown and Wickham in 1969 and later modified by Harrison and Constable in 1970. In 1976 Asmussen and Ulmsten described the use of microtransducers mounted on a semi-flexible Dacron catheter in female patients. Asmussen (1976), in a comparative study with the conventional open-ended catheter, found the microtransducer to be superior.

A new triple microtransducer catheter has been designed for male patients with a self-retaining mechanism—"The Baghdad modification". This instrument enables the pressure changes in the bladder, prostatic and bulbar urethras to be measured simultaneously, and recorded during bladder filling and during micturition.

Catheter Specifications

There are 3 microtransducers (Fig. 1). The first microtransducer is located at the catheter tip in order to measure the pressure changes in the bladder. The second and third transducers are located at 8 and 14 cm respectively, and measure pressure changes in the prostatic and bulbar urethra.

The catheter length is 50 cm, diameter 2.64 mm (8F), and it is covered with silicone rubber (Dacron was found to be unsuitable for the male urethra). The whole catheter consists of 3 tubes. A hollow tube is used to measure the residual urine and to infuse fluids. The second tube carries a wire that can be made to bow out (or collapse) by pushing a metal cap at the distal end of the catheter (Fig. 2). The third tube carries the necessary electrical connections to the 3 transducers.

Patients and Methods

Twelve patients were studied and were divided into 2 groups.

In Group I, 9 patients with bladder neck obstruction were examined. In Group II, 3 patients with obstruction at the distal urethral component or external sphincter were studied. In both groups, the patients were catheterised in a semi-sitting position and when the 3 transducers were located inside the bladder, the self-retaining wire was locked in position. The catheter was slowly withdrawn until the bowed out wire could be felt to impinge on the bladder neck. The bladder was then filled with normal saline at a rate of 50 ml/min. During filling the patient was asked to cough in order to detect any abnormal detrusor contraction or any urinary leakage. The patient was then asked to stand up and void when he felt the urge to micturate. Pressures were recorded during catheterisation, during catheter withdrawal and during micturition. The recordings were made on a Mingograph Machine Mark 82.

Results

The catheter tracing provided new data in many cases, so that a comparative study was carried out

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Read at the 34th Annual Meeting of the British Association of Urological Surgeons in Brighton, June 1978.

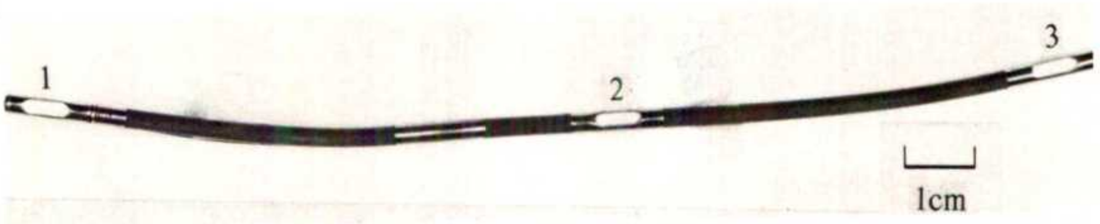

Fig. 1 The triple microtip pressure transducers: 1. bladder, 2. prostatic urethral, and 3. bulbar urethral transducers.

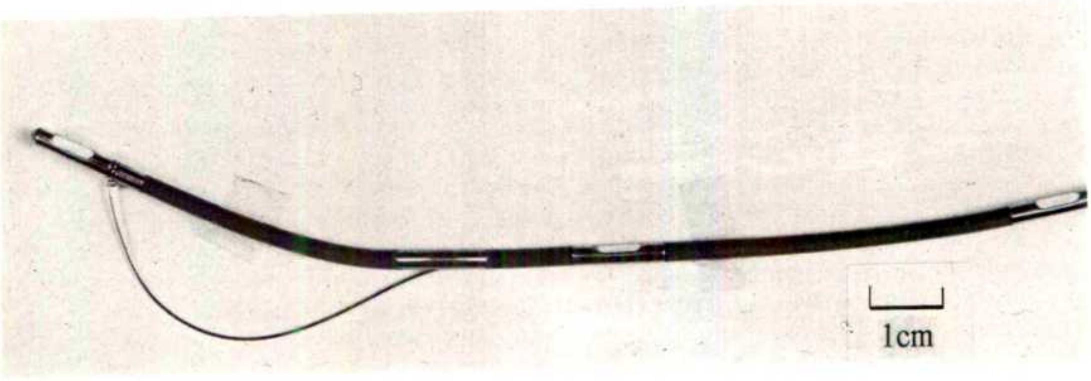

Fig. 2 The bowed out wire acting as a self-retaining mechanism.

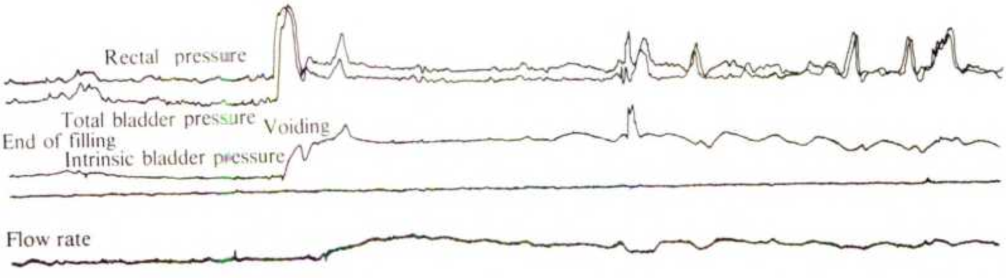

Fig. 3a *Patient 1.* Conventional cystometrogram and flow rate: a high intrinsic detrusor pressure coupled with poor flow rate, a picture of obstruction. (└──┘ represents a pressure of 40 cm H_2O.)

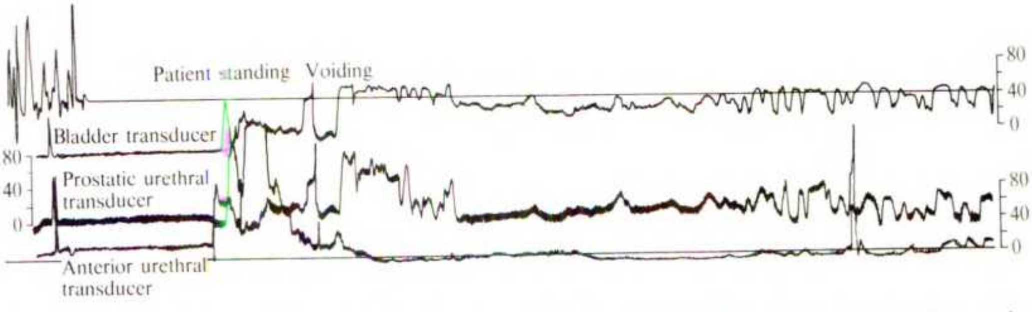

Fig. 3b *Patient 1.* Using the new catheter. A study of the pressure changes in the bladder, prostatic and bulbar urethra during micturition. There is a poor transmission of pressure between the bladder and the prostatic urethra, a picture of bladder neck obstruction. (└──┘ represents a pressure of 40 cm H_2O.)

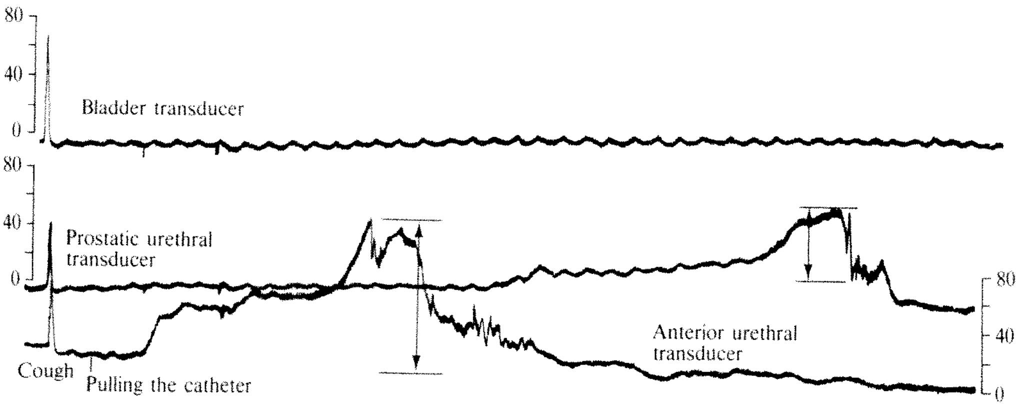

Fig. 4 Using the new catheter to measure urethral pressure profile from patient 2. Curve A represents the combined pressure exerted by the bladder neck and the external sphincter or the distal urethral component = 90 cm H_2O. Curve B represents the pressure exerted by the bladder neck only = 45 cm H_2O. By subtracting B from A = 45 cm H_2O, the net pressure exerted by the external sphincter or distal urethral component. (*Note:* There is no rise in the bladder pressure because the self-retaining mechanism has kept the first transducer inside the bladder.)

in each patient with a conventional cystometrogram and flow rate, and also with a videotaped filling and voiding cystourethrogram.

Example 1

A 60-year-old patient complained of hesitancy, urgency, nocturia and poor urinary stream. The IVU showed evidence of urinary outflow obstruction and the conventional cystometrogram and flow rate confirmed this (Fig. 3a). The videotaped filling and voiding cystourethrogram showed:
R_1 = 50 ml
Bladder capacity = 850 ml
End filling pressure = 10 cm H_2O
Voiding pressure = 40 cm H_2O
Peak flow rate = 18 ml/s
R_2 = 50 ml.

Using the new self-retaining catheter (Fig. 3b), there was a rise in the bladder pressure to approximately 40 cm H_2O while the pressure rise in the prostatic and bulbar urethra was negligible. There was poor transmission of pressure between the bladder and the prostatic urethra. The evidence indicated that this patient had bladder neck obstruction. After a transurethral resection of his prostate he voided urine satisfactorily.

Example 2

A 51-year-old patient was referred from the National Hospital for Nervous Diseases with frequency, urgency, urge incontinence, poor stream and intermittent urinary retention. The conventional cystometrogram and flow rate showed a picture of instability and obstruction. The videotaped filling and voiding cystourethrogram showed:
R_1 = 350 ml
Bladder capacity = 700 ml
End filling pressure = 80 cm H_2O (very unstable)
Voiding pressure = 45 cm H_2O (falling and decompensated)
Peak flow rate = 7 ml/s
R_2 = 300 ml
No milking.

The diagnosis was made of bladder decompensation due to outflow obstruction, probably at the external sphincter.

The self-retaining catheter was used to check the patient's urethral pressure profile (Fig. 4). The result of the pressure profile was compared with that obtained from a normal volunteer (Fig. 5). The pressure exerted by the distal urethral

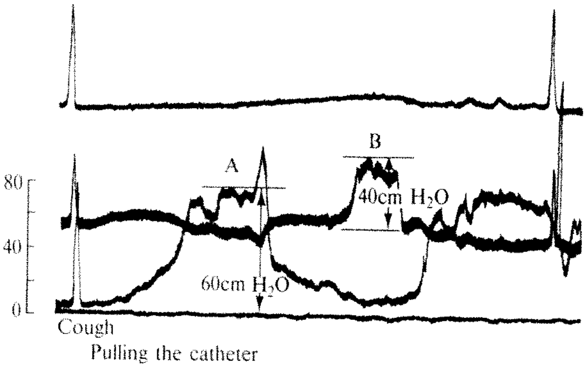

Fig. 5 Urethral pressure profile in a normal volunteer: subtracting B from A gives external sphincter pressure of 20 cm H_2O.

component or external sphincter in this patient was 45 cm H_2O, which may be compared with a pressure of 20 cm H_2O exerted by the distal urethral component or external sphincter in the normal volunteer. The 45 cm H_2O pressure exerted by the distal urethral component or external sphincter in this patient was considered abnormally high; he had external sphincterotomy and thereafter he voided satisfactorily with only 50 ml residual urine.

Conclusion

Preliminary results indicate that this new triple pressure recording catheter can give accurate information on pressure changes in the bladder, prostatic and bulbar urethra during micturition, and also provides a urethral pressure profile.

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Results of Transurethral Resection of Prostate in Patients with Cerebrovascular Disease

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Summary—Twenty-two patients with bladder outflow obstruction and a past history of cerebrovascular accident are described. Sixteen patients regained normal micturition control. Poor results occurred in the more handicapped patients, especially in those with additional neurological problems.

Patients who present with bladder outflow obstruction should be treated surgically. To determine those patients who will have a poor result full clinical and neurological assessment must be made, together with urodynamic studies. In order to improve these results a team approach is required between the urologist, geriatrician, nurse and physiotherapist.

The development of safer anaesthesia and improvements in transurethral surgical techniques have brought many more patients with general medical conditions within the scope of surgical correction of bladder outlet problems. Patients with neurological disorders form a special group, as both detrusor and sphincter function may be abnormal as a direct result of the neurological condition. In the past many patients have been turned down for prostatic surgery as they had suffered a previous cerebrovascular accident. However, with increasing ageing of the population more of these patients are presenting for surgery. The validity of surgery for patients with advanced vascular disease has been recently questioned (British Medical Journal, 1978).

The post-operative functional result may be unsatisfactory because of incontinence or further retention of urine, due to the effect of the neurological deficit on the micturition mechanism or on the higher cerebral functions, reducing the patient's capability of understanding the situation and the ability to regain micturition control. These patients may require a long post-operative period in hospital before becoming continent of urine or may require long-term catheter drainage. With these factors in mind we have evaluated our results of transurethral resection of the prostate in these patients.

Patients and Methods

In the 5-year period from 1972 to 1976, 22 patients aged 58–93 years with a past history of cerebrovascular accident presented for transurethral resection of the prostate. All patients were admitted under one surgeon (RWMR) and operated upon by himself or the First Assistant. The urological presentation was retention of urine in 16 patients (acute in 13, chronic in 3), incontinence of urine in 3 patients and symptoms of outflow obstruction in 3 patients.

Fourteen patients had suffered a stroke within 2 years prior to surgery, the remaining 8 patients between 2 years and 11 years previously. Overall the left and right sides were equally affected. At the time of surgery 11 patients had absent or minimal neurological signs, 7 patients had moderate residual signs and 4 patients had a dense hemiplegia.

Twenty patients had a general anaesthetic and 2 patients had a spinal anaesthetic. There was no per-operative mortality.

The histology in all patients showed benign disease of the prostate.

Results

Ten patients who had made a good recovery from the cerebrovascular accident and had no other medical problems, had a good result after transurethral resection, developing full micturition control. Five patients with only partial recovery also developed full micturition control. These patients

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were generally well and had no other neurological deficit apart from the hemiparesis. One other patient with a dense right hemiplegia due to internal carotid artery occlusion also made a satisfactory recovery (Table 1).

Table 1 Post-operative Micturition Control

Post-operative Micturition Control	*Recovery from CVA*		
	Poor	*Partial*	*Good*
Poor	2	3	1
Good	1	5	10

The significant post-operative complication was urinary incontinence, present in 13 patients. Of these 7 became continent on strict bladder training and using anal plug electrode continence devices. The remaining 6 patients were resistant to treatment and required an indwelling urethral catheter or an incontinence appliance.

Six patients had a poor result (Table 2). These all had poor recovery from the cerebrovascular accident and additional medical problems: severe Parkinson's disease in 2 patients, post-operative extension of the cerebrovascular accident in 2 patients, and dysphasia and communication difficulties in 2 patients. There were good indications for these patients undergoing surgery: inability to replace a urethral catheter in 2 patients, severe outflow symptoms in 2 patients and haematuria and urinary retention in the remaining 2.

The length of the post-operative stay in hospital was related to the time taken for the patient to regain normal micturition control (Table 3). As previously shown, post-operative incontinence is higher than would be expected in otherwise fit patients, the average inpatient stay being prolonged. Fourteen patients were discharged in under 15 days, all except one having a good functional result. This patient had a post-operative confusional state, took his own discharge from hospital and had a poor result with urinary incontinence. Of the 8 patients who stayed in hospital over 25 days, 3 regained micturition control at 28 days, 30 days and 45 days respectively. Two of these had only partial recovery following the cerebrovascular accident, the other a good recovery.

Table 3 Length of Post-operative In-patient Stay

Days	5–9	10–15	25+
No. of Patients	8	6	8

Discussion

The effect of a cerebrovascular accident upon the bladder may be varied, disturbing both the inhibition of the motor cortex on the sacral micturition centre and the sensory awareness of bladder fullness. These neurological disorders may cause detrusor hyperreflexia (Dam *et al.*, 1976) resulting in urinary frequency, urgency and incontinence, mimicking symptoms of bladder outflow obstruction. Anderson and Bradley (1976) have shown a high incidence of detrusor hyperreflexia in patients with Parkinson's disease, more than half of the patients in their series showing typical changes on cystometry. Mild or severe detrusor instability may be secondary to outflow tract obstruction, frequently resolving after relief of the obstruction (Turner-Warwick *et al.*, 1973). Urodynamic studies would make an accurate diagnosis of detrusor function and the level and degree of obstruction, making it possible to distinguish the neurogenic from the obstructed bladder.

The combination of a cerebrovascular accident

Table 2 Poor Results following Transurethral Resection of Prostate

Patient	*Age (yrs)*	*Recovery from CVA*	*Other medical problems*	*Indications for Surgery*
R.A.	79	Poor	Dysphasia. "General debility"	Unable to replace long-term urethral catheter
H.L.	77	Partial	Extension of CVA post-op.	Severe symptoms
E.L.	72	Poor	Dysphasia. Communication problems	Urinary retention
W.H.	63	Partial	Extension of CVA post-op. Confusional state	Severe symptoms
N.G.	80	Partial	Severe Parkinson's disease	Haematuria. Urinary incontinence
W.F.	68	Partial	Severe Parkinson's disease. Dysphasia	Unable to replace long-term urethral catheter

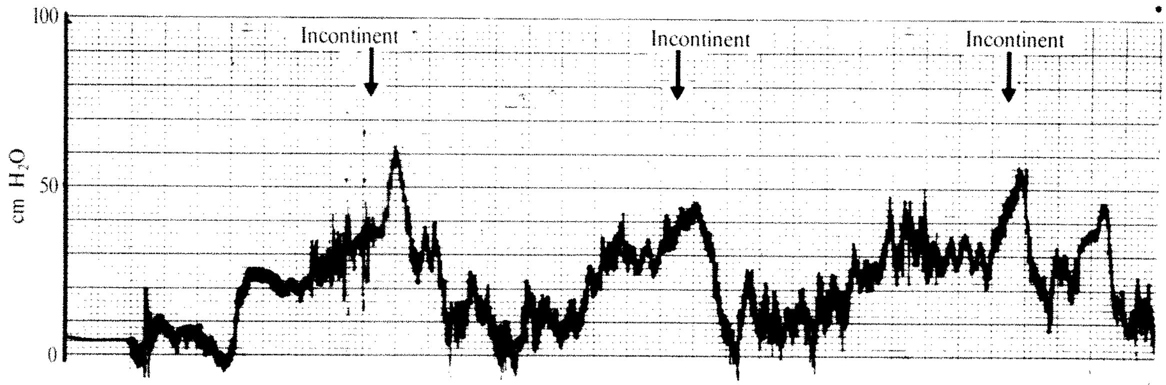

Fig. Cystometrogram of patient with incontinence; subtracted detrusor pressure. Capacity 100 ml.

and Parkinson's disease requires full urodynamic studies in those patients who present with outflow tract symptoms or urinary incontinence, so that conservative management may be considered when a neurogenic bladder is diagnosed (Fig.).

The patients in our series with a neurological disorder and bladder outflow obstruction have shown good post-operative results. The clinical impression in the patients with poor results indicates that in 3 of them a better result would have been expected. In 2 patients with severe symptoms, a further mild cerebrovascular accident may have compromised the result; a pre-operative urodynamic assessment would have been useful and this has become a routine investigation in this type of patient. The third patient had urgency of micturition and a dense hemiplegia, with dysphasia making communication difficult. The combination made it impossible for him to obtain and use a suitable receptacle before voiding occurred. A pre-operative functional assessment by an occupational therapist would be useful in such a case. The remaining 3 patients with poor results had severe and mixed neurological disorders. All the other patients had satisfactory post-operative results, including patients with moderate to severe disability. As handicapped patients are much more easily nursed at home, catheter-free, a careful search must be made for those patients who could be helped by surgery.

The high incidence of post-operative incontinence of urine may be due to detrusor dysfunction or reduced cerebral control of micturition. All patients should have strict and, if necessary, prolonged bladder training encouraged by the nursing staff. The additional use of anal plug electrode continence devices further aids the post-operative recovery (Hopkinson and Lightwood, 1967), but not all patients can tolerate the device. Post-operative urodynamic studies may indicate detrusor instability and additional drug therapy be instituted.

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A Critical Evaluation of the Results of Transurethral Resection of the Prostate

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Summary—In a review of 1057 consecutive prostatectomies of which 95% were performed transurethrally, carcinoma was present in 11.8%. There were 10 deaths within a month of operation (0.9%), 9 of these patients having been exceptionally old and unfit. The rate of complications and the end results appear to justify using transurethral resection as the method of choice for prostatectomy whenever it is feasible.

Six years ago evidence was presented to this association that the removal of the prostate transurethrally could give results which were not worse than those of open operation (Singh *et al.*, 1973). Since that time, fibre lighting and the Hopkins rod-lens telescope have made transurethral resection much easier, with the result that any form of open prostatectomy is now relatively rare in our practice. The question must now be asked, "Have we gone too far? Are we now doing too many TURs?"

We thought it high time to audit our results in an attempt to answer this question. Accordingly we have reviewed all prostatectomies done under our care at the London and St Peter's Hospitals between 1972 and 1976—a 5-year period during which many of the operations were performed by senior registrars in training.

Patients and Methods

One thousand and fifty-seven consecutive cases were reviewed. They had been admitted to the London Hospital, or under one of the authors to St Peter's Hospital, between January 1972 and December 1976. The indications for prostatectomy were the usual ones (Blandy, 1978a): 34.5% required prostatectomy because of acute retention, and a further 9.6% were admitted with the distended bladder and large residual urine typical of chronic retention (Table 1).

Table 1

	TUR (%)	*Open (%)*	*Total (%)*
Acute retention of urine	346 (34.5)	19 (35.8)	365 (34.5)
Chronic retention of urine	95 (9.5)	7 (13.2)	102 (9.6)

The age distribution of these patients (Table 2) is that usually found in prostatic enlargement: carcinoma was present in 11.8% of patients (Table 3), uraemia in 16.3% (Table 4) and in 15.9% of the entire group the urine was infected by the time they came to operation.

Ninety-five per cent were operated on transurethrally, 51 by the retropubic and 2 by the transvesical method. The weight of tissue removed is shown in Table 5 and Figure 1, in which it is seen that open operation was restricted to cases with the particularly large glands.

To evaluate the results it is necessary to take into consideration the general medical condition of the patients in this series, bearing in mind that the majority were operated on at the London Hospital, which serves a notably poor and underprivileged population, and that in 91 cases the

Table 2 Age Distribution of Patients at Prostatectomy

Age (years)	*No.*	*(%)*
41-50	27	2.6
51-60	157	14.8
61-70	504	47.7
71-80	291	27.5
81 +	78	7.4
Total	1057	100

Read at the 34th Annual Meeting of the British Association of Urological Surgeons in Brighton, June 1978.

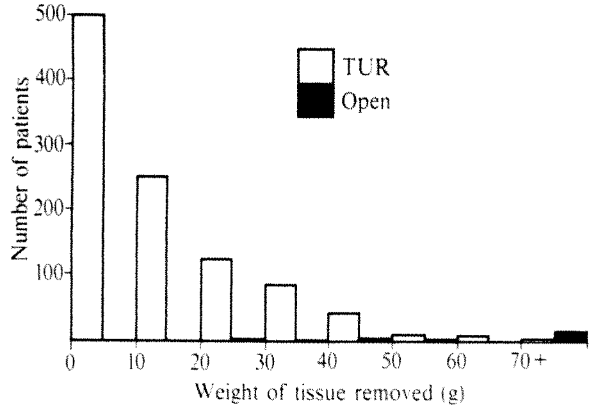

Fig. Method used in 1057 consecutive prostatectomies 1972 to 1976.

indication for prostatectomy was retention arising after some other major surgical or medical condition had led to admission to hospital. We have again used the grading system we described in detail (Singh *et al.*, 1973). Grade 1 included men under 70 years of age without obvious cardiovascular or respiratory disease or diabetes, and in good general condition. In Grade 2 were men with moderate to severe diabetes, hypertension, chronic bronchitis and emphysema, previous coronary thrombosis or stroke more than 6 months ago, and aged between 71 and 80. In Grade 3 were men over 81 years of age and those with a recent cardiac infarct, a stroke, pneumonectomy, abdominoperineal resection, and those with pacemakers *in situ*. Prostatectomy was withheld only under the most extreme circumstances, mainly if a patient was demented or confined to bed with widespread metastases. Often the important motive for performing the prostatectomy was that a geriatric unit would not accept the patient while he had an indwelling catheter. In the period under review fewer than 0.5% of patients with an index diagnosis of prostatic enlargement were discharged with a catheter.

Transurethral resection was performed by a more or less uniform technique (Blandy, 1978b), and by consultants and senior urological registrars.

Table 3 Histological Findings in 1057 Prostatectomies

Histology	*TUR (%)*	*Open (%)*	*Total (%)*
Benign	881 (87.7)	51 (96.2)	932 (88.2)
Malignant	123 (12.3)	2 (3.8)	125 (11.8)

Table 4 Blood Urea Before Prostatectomy in 1057 Cases

Blood urea mg/dl	*TUR (%)*	*Open (%)*	*All cases (%)*
Under 50	844 (84.1)	41 (77.4)	885 (83.7)
51-100	109 (10.8)	6 (11.3)	115 (10.9)
101+	51 (5.1)	6 (11.3)	57 (5.4)
Total	1004 (100)	53 (100)	1057 (100)

Results

Operative Mortality

There were 10 deaths in 1004 TURs (1.0%) and none in the 53 open cases. Nine of these deaths were in Grade 3 patients: 3 from heart failure, 2 from a stroke and 4 from pneumonia. One unexpected death was seen in a 68-year-old Grade 1 patient who was manic depressive and medicated with lithium, phenformin and imipramine, who died 18 h after TUR. No cause of death could be found even at post-mortem examination.

Late Mortality

Eight more patients died within the second and third month from operation, all from extensive carcinomas (3 of the prostate, 3 of the bladder, 1 of the stomach and 1 of the kidney).

Perforation

Perforation requiring open drainage of the retropubic space was seen in 4 cases (0.4%), none of which suffered any serious consequence. *Secondary haemorrhage* necessitating readmission of the patient and his return to the operating theatre for evacuation of clot was seen in 21 cases (2.1%) and was fatal in none of them. *Pulmonary infection* was noted in 40 cases (4.0%) of the TURs,

Table 5 Weight of Prostate Removed

Grams	*TUR (%)*	*Open (%)*	*All cases (%)*
< 10	449 (44.7)	0 (0)	449 (42.5)
– 20	254 (25.3)	0 (0)	254 (24.0)
– 30	122 (12.2)	3 (5.7)	125 (11.8)
– 40	83 (8.3)	2 (3.8)	85 (8.0)
– 50	48 (4.8)	8 (15.1)	56 (5.3)
– 60	19 (1.9)	7 (13.2)	26 (2.5)
– 70	15 (1.5)	3 (5.7)	18 (1.7)
> 70	7 (0.7)	28 (52.8)	35 (3.3)
no data	7 (0.6)	2 (3.8)	9 (0.9)
Total	1004	53	1057

Table 6 Operative Mortality and Clinical Grade

Clinical grade	*No.*	*Deaths*	*(%)*
1	463	1	0.2
2	380	0	0
3	161	9	5.6
All TURs	1004	10	1.0

and 6 (11.3%) of the open cases, but clinical evidence of pulmonary embolism was found in only one of the TURs—a rare complication as has been noted previously (Singh *et al.*, 1973; Hedlund, 1976; Lund and Dingsør, 1976). *Urinary infection* was still common in this series (Table 8), nearly 1 in 5 of those coming to operation with sterile urine getting infected afterwards. Fortunately the serious sequelae of infection were rare, epididymitis occurring in only 4 patients in the TUR series, and septicaemia in 18 (Table 9). If patients are excluded in whom *incontinence* was obviously related to underlying neuropathic lesions, or to infiltration of the external sphincter by carcinoma, then true surgically-induced incontinence persisting for more than 3 months was seen after TUR in 0.5%, but in addition to these a further 1.5% complained of slight urge incontinence and minor degrees of "dampness" (Table 10). *Stricture* still appears to be an important complication of prostatectomy, not limited to TUR: most common were the external meatal strictures which responded to a few dilatations in the post-operative period, and were not important. More serious were those for which regular intermittent dilatation or a urethroplasty was required, and these were seen in 1.2% of TURs and 3.8% of open operations (Table 11).

Revision

In the period under review 51 men had to have another resection (5.1%), among whom were 9 with carcinoma. In none of these cases was the second resection followed by any serious or fatal sequelae. In addition there were 53 patients in this series who had had a previous prostatectomy elsewhere or more than 2 years previously, among whom were 11 who had undergone an enucleative open operation.

Table 7 Complications of TUR

Perforation needing exploration and drainage	4	0.4%
Secondary haemorrhage needing evacuation	21	2.1%
Pulmonary infection	40	4.0%
Pulmonary embolism	1	0.1%
Stroke	6	0.6%
Coronary thrombosis	3	0.3%

Table 8 Urinary Infection After Prostatectomy

Urine culture		*TUR (%)*	*Open (%)*	*Total (%)*
Pre-op	*Post-op*			
Infected	Sterile	48 (4.8)	2 (3.8)	50 (4.7)
Sterile	Infected	191 (19.1)	25 (47.2)	216 (20.4)
Infected	Infected	116 (11.6)	2 (3.8)	118 (11.2)
Sterile	Sterile	649 (64.6)	24 (45.3)	673 (63.7)
Total		1004 (100)	53 (100)	1057 (100)

Table 9 Infective Complications After Prostatectomy

	TUR (%)	*Open (%)*	*All cases (%)*
Epididymitis	4 (0.4)	1 (1.9)	5 (0.5)
Septicaemia	18 (1.8)	1 (1.9)	19 (1.9)

The Patient's View of the Operation

The patient's view of an operation is notoriously fallacious; nevertheless the observations recorded in this series (Table 13) are not significantly worse than those cited in other comparable series: more than 90% said they were much better or were cured.

Discussion

Over the last 5 years the proportion of prostatectomies operated on transurethrally has increased from 81 to 95% in our practice, with more and more of the larger glands being removed endoscopically. During this time the mortality has decreased from 1.4 to 1%, and is now almost restricted to those who are very old and already very ill. Sach and Marshall (1977) have remarked on the special hazard of prostatectomy in the very old, and it must always call for the nicest

Table 10 Post-operative Incontinence of Urine in Benign Glands (932 cases)

	TUR	*Open*	*Total (%)*
Incontinent	5	0	5 (0.5)
Slight symptoms	14	0	14 (1.4)
Total	19	0	19 (1.9)

Table 11 Post-operative Stricture After Prostatectomy

	TUR (%)	*Open (%)*	*All cases (%)*
Temporary	8 (0.8)	3 (5.7)	11 (1.0)
Permanent	12 (1.2)	2 (3.8)	14 (1.3)

judgement to decide when to operate and when to refrain, but it is as well to recall that Ashley *et al.* (1971) found a 37% early mortality among the 18.9% of men admitted to non-urological centres who had been considered unfit for prostatectomy. Shortage of surgical beds and long waiting lists may perhaps have led to some unnecessary operations, as in those 8 men who succumbed to their other cancers within 3 months of prostatectomy; nevertheless they were able to go home, or to another long-stay hospital without a catheter.

The complication which gives us most concern is the persistently high rate of post-operative infection. Our rate of 19.1% is a good deal lower than that found by Islam and Chapman (1977), but it gives us no room for complacency. The low incidence of epididymitis in this series (0.4%) suggests again that routine division of the vas is today an unnecessary feature of prostatectomy. It was done in none of these cases.

In this series antibiotics were in general only given when patients had a known previous urinary infection, as a safeguard against bacteraemia, or when their pulmonary infection demanded it. There was a 1.8% incidence of septicaemia, mainly seen in patients in whom it was most unexpected, and it seems doubtful if more vigorous prophylactic antibiotics would diminish this incidence.

Patients admitted with acute retention during this period were catheterised and put on the next convenient operating list. Suprapubic catheterisation was only used when it was found impossible to pass the catheter *per urethram*. Since the proportion of those admitted in acute retention who left hospital with infected urine is no different from those who were admitted from the cold waiting list, we remain sceptical that routine suprapubic catheterisation would have lowered the rate of infection.

Table 12 Revision Prostatectomy

	TUR	*Open*	*All cases*
Within first 3 months	21 (4 Ca) 2.1%	0	21
4-12 months	30 (4 Ca) 3.0%	0	30
1-10 years	50 (8 Ca) —	11	61

The incidence of stricture noted in this series is probably falsely low, for unless the patients had symptoms they were not investigated by urethrography or the passage of a bougie. It will be recalled that Lentz *et al.* (1977) found that 9% of their cases could be shown to have a post-operative stricture.

In recent years the ancient operation of prostatotomy has been revived, and claims have been made that endoscopic incision of the bladder neck gives results which are superior to conventional TUR, particularly in respect of the prevention of retrograde ejaculation. A surprising number of our patients appear to have unaffected ejaculation and orgasm, despite a thorough resection, and as for the effect on the patient's symptoms, since 499 of the present series had less than 10 g of tissue removed, and appear to have had excellent results, we continue to doubt whether the results of incision of the bladder neck are really any better.

It remains true that any operation to remove benign adenoma which does not remove the entire capsule of the prostate must carry a certain risk of regrowth of adenoma from the residual healthy prostatic tissue, and it is even more certain that the beginner is apt to leave prostatic tissue behind. Nevertheless the extra safety and freedom from morbidity of transurethral resection more than compensate for the need for an occasional revision of the resection. The difficulty of resecting the large gland will always impose an upper limit on the resectionist, and there will undoubtedly always remain the rare, very large adenomas, for which an open operation is necessary. The majority of prostatectomies can be done transurethrally: to achieve these results, however, protracted apprenticeship is necessary and a dedication to the speciality of urology. Transurethral resection is not an operation for the occasional operator.

Table 13 The Patient's Opinion of the Result of Prostatectomy

	TUR (%)	*Open (%)*	*All cases (%)*
Cured	701 (69.8)	47 (88.7)	748 (70.8)
Better	223 (22.2)	6 (11.3)	229 (21.7)
The same	59 (5.9)	0 (0)	59 (5.6)
Worse	21 (2.1)	0 (0)	21 (1.9)
Total	1004	53	1057

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Dicynene in Transurethral Resection of the Prostate

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Summary—A double blind trial of the haemostatic drug Dicynene has shown no beneficial effect in transurethral resection of the prostate.

There have been many studies of the effects of various haemostatic agents in prostatic surgery. Only 2 agents have produced positive results. Epsilon aminocaproic acid (Epsikapron) reduced the post-operative blood loss to 25% of that in controls (McNicol *et al.*, 1961), but had no effect on per-operative blood loss (Madsen and Strauch, 1966). Several reports have confirmed these results. Ethamsylate (Dicynene) reduced both per-operative and post-operative blood losses, but with caudal epidural being used in addition to general anaesthesia (Symes *et al.*, 1975).

Dicynene is a synthetic non-hormonal substance whose mode of action is not fully understood. Effects which have been demonstrated experimentally include an increase in platelet adhesiveness, a decrease in capillary fragility, and an increase in rate of release of intrinsic thromboplastin. Dicynene has been shown to reduce capillary haemorrhage under strictly controlled experimental conditions in pigs (Deacock and Birley, 1969). Blood loss from laparotomy wounds was reduced to less than half of that in controls, but only when the systolic blood pressure had fallen by more than 40 mmHg as a result of anaesthesia (Arnot *et al.*, 1975). A small beneficial effect was noted in cataract surgery (Hypher and Carpenter, 1968). In pterygoid space and middle ear microsurgery under strictly controlled hypotension, a dramatic reduction in troublesome oozing was noted in 4 out of 16 cases after the administration of Dicynene (Boyd, 1969). No beneficial effect was found in dissection tonsillectomy with standard general anaesthesia (Gray and Noble, 1966).

The present trial was designed to test the effect of Dicynene in transurethral resection of the prostate, in the absence of any other technique intended to reduce blood loss, and also to assess its safety with regard to venous thrombosis, by means of the ^{125}I-fibrinogen test.

Patients and Methods

One hundred patients were selected for the trial. The majority were undergoing routine prostatic surgery; a few had been admitted with acute retention and were catheterised shortly before surgery. Excluded were those with long-term indwelling catheters, chronic retention of urine, carcinoma of the prostate and small prostates (*i.e.* requiring a bladder neck resection only). The nature of the study was fully explained to each patient, and only after giving consent was the patient admitted to the trial. Treatment packs were prepared by the manufacturer in the form of blank ampoules in numbered boxes, with random distribution of Dicynene and Placebo. At no time did any of the operators know the nature of the contents of the treatment packs they were using, and the code was broken only when the trial was finished. Six of the studies were abandoned. In 5, the operative procedure was altered after the initial dose had been given, and in one the urine collection was accidentally discarded.

Sixty-five patients were investigated for deep vein thrombosis using the ^{125}I-fibrinogen test. Measurements were made with a Pitman 235 isotope localisation monitor at marked sites on each leg, 5 cm apart, pre-operatively, and on each post-operative day. The result was considered positive if there was a sustained rise in activity of 20% or more, at one or more sites, and equivocal if there was a definite rise in activity which did not quite reach the 20% level.

Anaesthesia was general and not standardised. The use of opiates and phenothiazines in premedication, and halothane and controlled ventilation during the operation, was noted, as any of these can produce hypotension and therefore influence blood loss.

Read at the 34th Annual Meeting of the British Association of Urological Surgeons in Brighton, June 1978.

The operations were carried out by 2 consultants and a senior registrar. The initial dose of trial substance (250 mg if Dicynene) was given intravenously in the anaesthetic room. All the irrigation and wash-out fluid was collected in a calibrated container. Blood-stained drapes were soaked in water at the end of the operation, and the eluent added to the main collection. Operations were timed from the start of the resection to the connection of the urine drainage bag, at which time the post-operative collection was commenced. The prostatic chips were weighed. The remainder of the trial pack was given, one ampoule at a time at 6 and 12 h post-operatively. The post-operative collection was continued for 48 h.

At the end of the per-operative and post-operative collections, the volumes were made up to the nearest litre, and the containers shaken vigorously to ensure homogeneity of the contents. Samples were taken, and in the laboratory small amounts were mixed with Drabkin's solution to produce cyanmethaemoglobin. The volumes were adjusted to obtain a suitable reading on a Linson 3 absorption spectrophotometer. Blood loss was calculated according to the formula:

$$\text{Blood loss} = \frac{0{,}02AB}{CD}$$

where A – reading on haemoglobinometer in grams per 100 ml.
B – total volume of collection in ml.
C – venous haemoglobin concentration in grams per 100 ml; pre-operative sample for post-operative loss; 2-day post-operative sample for post-operative loss.
D – volume of fluid assayed in Drabkin's solution in ml.

Results

The variables which could influence blood loss were evenly distributed between the Dicynene and Placebo groups (Table 1). There is a small difference in the mean weight of prostatic tissue resected in favour of the Dicynene group, which has the smaller value.

The per-operative blood losses were similar in the 2 groups and tended to fall within the range 0 – 400 ml, although larger losses occurred in a few patients (Fig. 1). In the case of the post-operative losses, there was a wider scatter in the

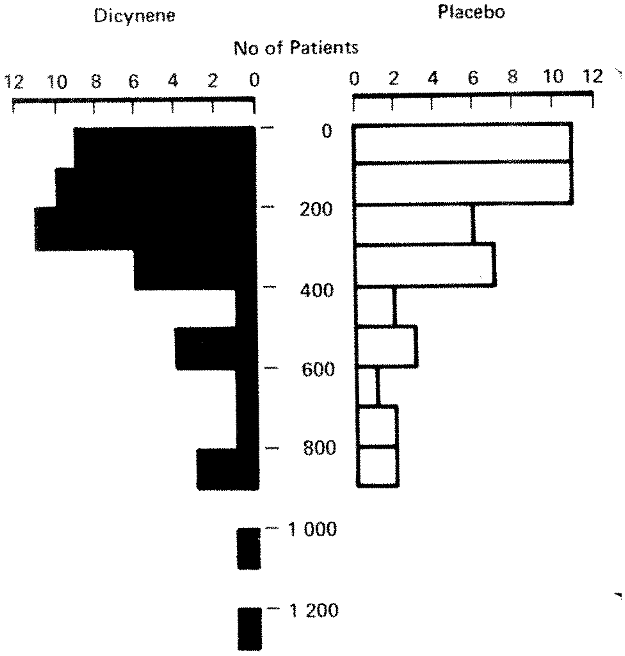

Fig. 1 Operative blood loss (ml).

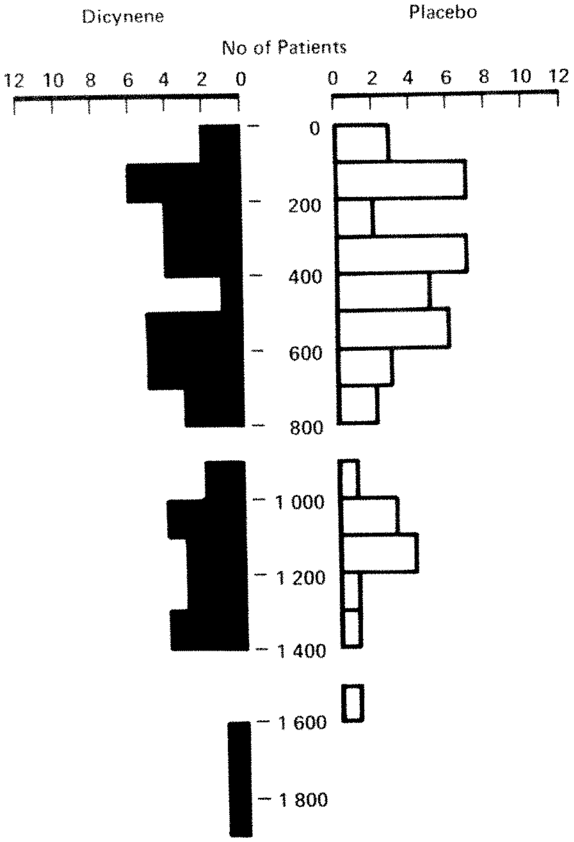

Fig. 2 Post-operative blood loss (ml).

individual results (Fig. 2). The effect of the scatter is seen in the large standard deviations (Table 2). The skewing effect can be reduced by taking $\log_{10}$. Whichever way the results are expressed, there is no significant difference between the Dicynene and Placebo groups with regard to either per-operative or post-operative loss.

Table 1 Comparison of Variables Which Could Influence Blood Loss

	Dicynene	*Placebo*
Age	71	72
Hypertension (diastolic B.P. >100 mm Hg no. of patients)	16	11
Urinary infection (no. of patients)	9	8
Opiate premedication (no. of patients)	11	15
Phenothiazine premedication (no. of patients)	8	6
Halothane (no. of patients)	41	40
Controlled ventilation (no. of patients)	21	20
Mean operating time (min.)	26	27
Mean weight of prostate (g)	13	18
Transfusion (no. of patients)	24	24
Units of blood transfused	2,2	2,1

The results of the ^{125}I-fibrinogen test showed an overall incidence of venous thrombosis of 8%, with no significant difference between the 2 groups. (Table 3). There were no clinically evident pulmonary emboli in any of the patients.

Table 2 Mean Blood Loss in ml (±s.d.)

	Per-operative	*Post-operative*
Dicynene		
Mean loss (ml)	326 (±227)	803 (±703)
$\log_{10}$	2.334 (±0.457)	2.757 (±0.383)
Placebo		
Mean loss (ml)	273 (±232)	618 (±507)
$\log_{10}$	2.233 (±0.493)	2.644 (±0.392)

Table 3 Results of ^{125}I-Fibrinogen Test

	Dicynene	*Placebo*
No. Tested	31	34
Equivocal	2	0
Positive	1	4

Discussion

Although the operative and anaesthetic conditions were not standardised, there were sufficient numbers in the trial to produce even distribution of variables. If the routine use of a haemostatic agent in prostatic surgery is to be justified, it should be able to produce marked reductions in blood loss and reduce the need for transfusion. It should also be completely safe with regard to venous thrombosis.

Dicynene is essentially an agent that decreases blood loss from capillaries and it may well have a use where capillary haemorrhage is a problem, as in microsurgery of the middle ear. It has not been shown to have any beneficial effect in the present trial, although the initial dose provided by the manufacturers was lower than is sometimes recommended. The study demonstrated that there was no increase in the incidence of deep vein thrombosis associated with the administration of Dicynene, and this confirms previous clinical impressions.

It is concluded that in the dosages recommended by the manufacturer for this trial, we cannot recommend the routine use of Dicynene in transurethral resection of the prostate.

Acknowledgements

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A Placebo-controlled Double-blind Study of the Effect of Phenoxybenzamine in Benign Prostatic Obstruction

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Summary—A double-blind placebo-controlled study of phenoxybenzamine for the symptomatic treatment of benign prostatic obstruction is reported.

Statistically significant evidence of an improvement in both the peak and mean flow-rates was found. Both diurnal and nocturnal frequency were significantly diminished. Residual urine was unaffected, and the possible reasons for this are discussed.

Urethral pressure recordings confirmed the reduction in the closure pressure in the prostatic segment of the urethra.

It was concluded that there was good evidence that the treatment is effective.

As a result of our experimental findings that there exists a high alpha-adrenergic receptor activity in the enlarged human prostate, both in the capsule and in the adenoma itself (Caine *et al.*, 1975a), we suggested that alpha-adrenergic blockers such as phenoxybenzamine or phentolamine might be of clinical use in the medical management of certain groups of patients suffering from benign enlargement of the prostate. Our initial observations on this use were published in 1976 (Caine *et al.*, 1976) and we have continued to use phenoxybenzamine extensively in our department, in the conviction that we are benefiting many patients who are suffering from moderate prostatic obstruction but do not require operation. In 1977 Boreham *et al.* published the results of a pilot study on its use, in which they reported considerable symptomatic and objective urodynamic improvement in 59% of their patients.

However, as many authors, including ourselves (Caine *et al.*, 1975b), have stressed, conclusions as to the value of any medical treatment for benign prostatic obstruction are unreliable without a placebo-controlled study, even when using so-called objective criteria. The present double-blind placebo-controlled study was therefore undertaken in order to check the validity of our clinical impressions. This trial is still in progress but we report here on preliminary results.

Patients and Method

Fifty patients suffering from benign hypertrophy of the prostate who attended our out-patient department were included in the trial. All patients were accepted apart from those with any evidence of impaired renal function due to the prostatic obstruction, those with any history or clinical evidence of cerebral arteriosclerosis, or any who were judged to be unreliable. Each patient was given a numbered container in which were 30 capsules of either phenoxybenzamine 10 mg or an identical-looking placebo, and was asked to take one capsule morning and evening for 14 days. The key as to the nature of the capsules in each container was known only to the senior pharmacist, and was not revealed to the investigators until the conclusion of the trial. Each patient was examined prior to starting the trial, and again on the fourteenth day. The urethral pressure profile, using an Elema-Schönander Mingograph recorder with the appropriate special flowmeter transducer and amplifier, was measured on each visit, and the residual urine was also measured unless it was already known to be negligible from a previous post-voiding bladder film on intravenous urography. In view of the extreme fallibility of symptomatology, the only symptoms that were recorded were those capable of quantification, namely the average frequency of micturition by day and by night. The size of the prostate was assessed clinically by bimanual examination, as is our routine, not in anticipation of any variation in size, but to determine if any observed

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Read at the 34th Annual Meeting of the British Association of Urological Surgeons in Brighton, June 1978.

Table 1 Average Increase in Peak Flow Rate

	Placebo (25 cases)	*Phenoxybenzamine (24 cases)*
Absolute (ml/s)	1.2	6.2
Percentage	18.5	87.5

response to treatment bore a relationship to the prostatic size. Any side effects reported by the patients were noted.

Results

Of the 50 patients included in this phase of the study, it transpired on eventually breaking the code that 26 had received the placebo and 24 the phenoxybenzamine. Forty-nine patients completed the trial, one patient developing a cerebrovascular accident 4 days after commencing the capsules. This is the solitary case in which the code was broken before the end of the study, and it was an understandable relief to learn that he had received the placebo. Thus a comparison is possible between 24 patients receiving the active drug and 25 receiving the placebo.

The results obtained on the urinary flow examinations are summarised in Tables 1 and 2, from which it can be seen that there is a highly significant improvement in both the peak flow rate and the mean flow rate in the patients who received the phenoxybenzamine as contrasted with those who received the placebo (Figs. 1 and 2). On the other hand, there was no significant difference between the 2 groups with regard to reduction in the amount of residual urine (Table 3). In this table, the numbers in parentheses indicate the number of patients in each group with an initial residual urine of more than 5 ml, in whom a meaningful reduction is hence a possibility. Table 4 shows the improvement in day and night frequency in the 2 groups, taking as the criterion of improvement the ability to hold urine an hour or more longer during the day, and the necessity to pass urine one or more times less during the night. As can be seen, there is good evidence of an improvement in both of these in the treated group (Fig. 3). Side effects were reported in 11 of the patients receiving the phenoxybenzamine, and one receiving the placebo. These generally consisted of tiredness or slight dizziness. Two patients reported impaired ejaculation, 2 nasal stuffiness or dryness, and 1 difficulty with accommodation. In no case did these cause the patient to stop the medication.

Table 2 Average Increase in Mean Flow Rate

	Placebo (25 cases)	*Phenoxybenzamine (24 cases)*
Absolute (ml/s)	0.85	3.18
Percentage	30.4	81.9

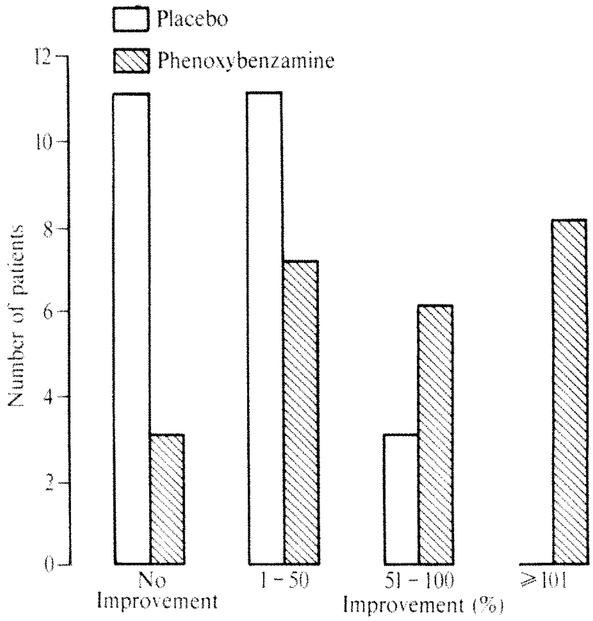

Fig. 1 Distribution of percentage improvement in peak flow rates.

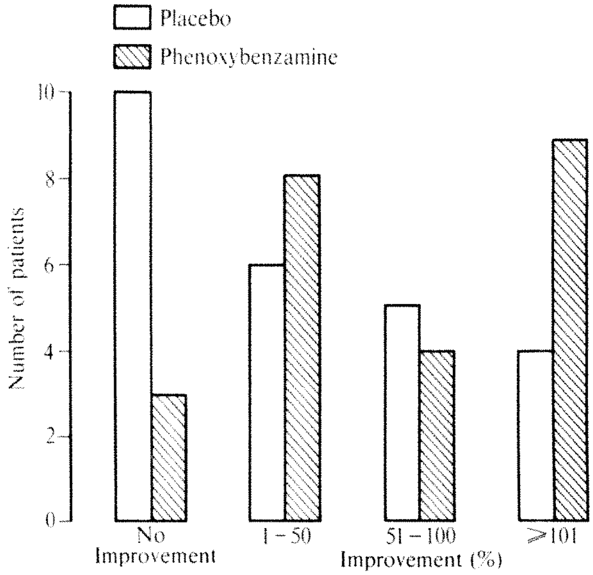

Fig. 2 Distribution of percentage improvement in mean flow rates.

Table 3 Reduction In Residual Urine

Reduction	*Placebo (19 cases)*	*Phenoxybenzamine (16 cases)*
25% or more	5	6
50% or more	3	4

Discussion

As the present trial was concerned with the pharmacological action on smooth muscle of a drug which is cumulative up to about 5 days, and not with an endocrinological action designed to reduce the size of the prostate, a period of 2 weeks was judged to be sufficient for any action to become manifest. Owing to the well-known spontaneous variations in the degree of prostatic obstruction, which we believe to be largely due to natural variations in the degree of alpha-adrenergic stimulation, an apparent response to placebo has often been noted in trials of drugs designed to help prostatic patients, and hence a properly controlled series such as the present one is essential in order to obtain reliable evidence and avoid being misled.

When comparing the urinary flows, 2 measurements were used—the peak flow rate and the mean flow rate. The former is probably the more reliable, as it is a clear-cut objective recording. The latter, although also reliable, is in some cases subject to a certain degree of uncertainty, as some patients may continue to express the last few drops of urine intermittently for a prolonged period of time, whilst others will declare themselves finished when they have passed the main quantity of urine. There may also be a degree of subjectivity in what is judged to be the exact end-point in such cases. However, insofar as all these estimations were made as objectively as possible by the same investigator, were decided upon before knowing the distribution of the patients, and hence applied equally to both groups of patients, these problems to a large extent cancel out, and the obvious and significant improvement in this parameter, as well as in the former, can safely be accepted as valid.

Table 4 Change in Frequency of Micturition

	Placebo	*Phenoxybenzamine*
Day frequency		
Improved	5	13
Not improved	20	11
Night frequency		
Improved	8	16
Not improved	17	8

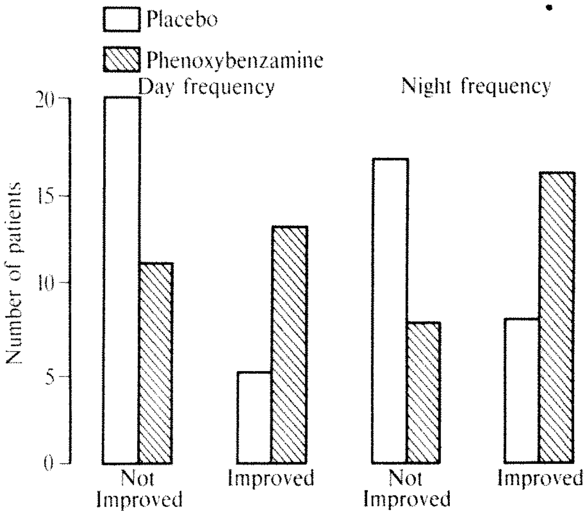

Fig. 3 Distribution of improvement in day and night frequencies.

Despite the well documented unreliability of symptoms, they cannot be ignored, for they are essentially what are being treated when operation is not performed. Use of the measurable symptoms of day and night frequency, together with the placebo controls, gives a reasonably acceptable assessment. The observed improvement in frequency is of particular interest in that, whereas the improvement in flow rate is a logical consequence of reduced urethral obstruction, a diminished frequency implies some effect on a hyperactive detrusor. We have previously remarked on this with regard to the increased volume of urine that patients receiving alpha-blockers appear to be able to retain and pass, and this raises the question as to whether the detrusor hyperreflexia is mediated in some way by the adrenergic nerves. We have noted an occasional example of detrusor hyperreflexia in prostatic cases, as demonstrated on the cystometrogram, being abolished by phentolamine.

The lack of any clear evidence of a reduction in residual urine is both striking and disturbing. However, it is possible that this particular feature is to some extent time dependent. The presence of residual urine indicates a degree of detrusor decompensation, and it may be that even though the outflow resistance is rapidly diminished, it will take longer than 2 weeks for this decompensation to improve. Moreover, it is possible that in the initial stage the alpha-blocker reduces the tone of the detrusor by acting on the alpha-receptors that, although relatively few in number, are none the less present in the detrusor above the bladder base (Awad *et al.*, 1974). Certainly, in patients treated for a longer period, we have seen many cases with a very significant reduction in residual urine.

That the administration of alpha-adrenergic blocking agents does indeed reduce the resting urethral pressure in the prostatic region has been confirmed on a number of occasions by urethral pressure profile recordings. Abrams (1976) has demonstrated the part played by the obstructing prostate on this examination, and we (Caine and Perlberg, 1977) have confirmed that the site of maximal obstruction in complete retention is in the region of the prostate. Thus a reduction in the intraurethral pressure in this region corresponds well to the improvement in the urinary flow rate observed in the treated patients.

In the present series, the full dose of 20 mg a day was maintained for the 2 weeks of the trial, and gave rise to side effects in an appreciable proportion of patients. It is worth recalling that in our ordinary clinical practice, in cases in which side effects are troublesome, we have usually found it possible to abolish these by reducing the dose to 10 mg a day, or even once every other day, without losing the beneficial effect of the treatment.

Although many patients receive definite benefit from this treatment, one cannot expect it to be equally effective in all cases. This will depend on the basal level of alpha-adrenergic stimulation of the prostatic muscle at the time of commencing the treatment and the relative roles played by this factor on the one hand and that of the basic mechanical obstruction of the tissue on the other.

It can be concluded that the present placebo-controlled study has confirmed that phenoxybenzamine is of practical value in the symptomatic treatment of many cases of benign prostatic obstruction.

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Serial Bone Scanning: The Assessment of Treatment Response in Carcinoma of the Prostate

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Summary—Serial bone scans and radiographic surveys were performed in 167 patients with histologically proven carcinoma of the prostate: 435 scans and surveys were performed. Nineteen of 99 patients with negative findings on diagnosis have become positive on follow-up. Forty-nine patients had positive findings on presentation; 8 have regressed on follow-up and 26 have progressed; 15 have remained unchanged.

This is a sensitive method of follow-up in patients with carcinoma of prostate. Changes occurred in bone scans and skeletal surveys before any alteration in serum acid or alkaline phosphatases, symptoms of metastases or change in prostatic size in the majority of cases.

The documentation of progression from M0 to M1 disease presents no problems. However, problems in quantitation may arise in patients presenting with M1 disease.

Although bone scanning is widely accepted as the most accurate method for the detection of skeletal metastases in carcinoma of the prostate (O'Donoghue *et al.*, 1978), its possible role in the objective assessment of the response to treatment has received relatively little attention. Robinson and Constable (1973) reported reduced uptake of isotope on follow-up studies following a satisfactory clinical response to hormonal therapy. Subsequently Shearer *et al.* (1974) described serial data on 30 patients using 87mStrontium which led them to suggest that failure of a positive scan to revert to normal after a period of adequate hormonal therapy may be an early indication of hormonal resistance. Buck *et al.* (1975) described serial studies and reported that bone healing following endocrine treatment was more readily apparent on X-rays than on scans, and that regression of scan abnormalities was unusual despite a favourable clinical and biochemical response.

Bone scanning in carcinoma of the prostate has been part of the routine investigation at St. Peter's Hospitals since 1969, and during that time a number of different isotopes have been in use, including 87mStrontium, Technetium-polyphosphate, Technetium-HEDP, and Technetium-MDP. The variety of isotopic agents reflects advances in radio-pharmacy, but has made the assessment of serial studies over this period particularly difficult.

We report a study to evaluate the role of serial scanning and radiographic surveys in the objective assessment of treatment response. The lack of acceptable objective criteria of response has been one of the principal difficulties in the organisation of controlled trials in carcinoma of the prostate.

Patients and Methods

A prospective study was commenced in January 1975 to evaluate serial bone scans and skeletal surveys in histologically proven carcinoma of the prostate. Bone scans were performed after the injection of 10 mCi of commercially available ^{99m}Tc-diphosphonate, and a Mark III Nuclear Enterprises Gamma Camera was used for imaging. The skeletal survey consisted of X-rays of the axial skeleton, chest and pelvis. All scans and surveys were reviewed jointly by a surgeon, a physicist and a radiologist. A negative result consisted of an absence of metastases in both scan and survey. A positive result meant a positive scan (having excluded benign bone disease), with or without a positive skeletal survey.

Serial bone scans and skeletal surveys have been performed on 167 patients. Each patient had a scan and survey before treatment, 6 months and a year after starting treatment, and every year

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thereafter. They were also performed more often if clinically indicated. The patients were interviewed at least every 6 months, and had a full physical examination, and serum acid and alkaline phosphatase estimations at each visit.

Results

Of the 167 patients who had serial bone scans and skeletal surveys, 19 patients were excluded because treatment had been started before the first examination. The remaining 148 patients were sub-divided into groups depending on the results of their scans and surveys:

Group I consisted of 80 patients whose scans and surveys were initially negative and remained negative (54% of the total). Group II consisted of 19 patients (13%) whose initial scan and survey were negative, but later became positive. Group III consisted of 34 patients (23%) whose initial scan was positive and then showed progression (26 patients) or regression (8 patients). Group IV consisted of 15 patients (22%) whose initial scan was positive and remained positive.

Groups II and III were examined further because they showed either progression or regression, and the changes in the scans and surveys could be compared to changes in the other indices. Of the 19 patients in Group II, progression from a negative to a positive scan and survey occurred with a normal acid phosphatase in 14 patients (74%); with a normal alkaline phosphatase in 15 patients (79%); with no symptoms of metastatic disease in 16 patients (84%); and with no concomitant increase in prostatic size in 18 patients (95%). These results are shown in Table 1.

Table 1 Changes Observed in Patients in whom Negative Scans and Surveys Became Positive (Group II)

Normal acid phosphatase	14/19 (74%)
Normal alkaline phosphatase	15/19 (79%)
No symptoms of metastases	16/19 (84%)
No alteration in prostatic size	18/19 (95%)

It is shown in Table 2 that progression or regression from an initially positive scan and survey occurred *without* alteration in acid phosphatase in 23 of 34 patients (68%); in alkaline phosphatase in 18 patients (54%); in symptoms in 30 patients (89%); and in changes in prostatic size in 30 patients (89%).

Table 2 Changes in Patients with Positive Scans and Surveys (Group III) Occurred without Alteration

Acid phosphatase	23/24 (68%
Alkaline phosphatase	18/34 (54%)
Symptoms	30/34 (89%)
Prostatic size	30/34 (89%)

It may be seen in Table 3 that changes were detected in scans and surveys in patients in Groups II and III *before* changes were detected in phosphatases, symptoms or prostatic size in 62–90% of cases.

Table 3 Combined Results on Groups II and III—Changes in Scan and Survey Preceded Changes

Acid phosphatase	37/53 (70%)
Alkaline phosphatase	33/53 (62%)
Symptoms	46/53 (87%)
Prostatic Size	48/53 (90%)

Discussion

The difficulties in formulating acceptable objective criteria of response to treatment in carcinoma of the prostate are well known. Many patients with early disease may be non-evaluable in that there are no convenient marker lesions which can be measured and biochemical tumour markers have been of little value. The assessment of primary tumour size by rectal assessment is subject to considerable observer error and is difficult to quantitate. In M1 or Stage D disease, however, the problem is rather more easy and most urologists would probably agree that in retrospect they can identify those patients who have fared well on hormonal therapy. The return of elevated acid and alkaline phosphatase values to normal, the resolution of hydroureter and hydronephrosis, the improvement of obstructive micturition symptoms, and the relief of bone pain, may all provide evidence of a favourable response. Although any one of these indices alone may provide unacceptable evidence of response, there is usually little doubt on retrospective review of the overall situation. It is in this light that we have assessed the value of serial scanning. In this study regression or progression of the disease was apparent on serial scans and surveys in the majority of cases before alteration in other indices.

In M0 disease, acid and alkaline phosphatases are unlikely to be elevated (O'Donoghue *et al.*,

1978) and are therefore unhelpful in assessing the response to hormonal treatment. One may therefore be left with rectal assessment of the T category as the only index of response with all the attendant problems of a subjective evaluation. The metastases-free interval may be a more useful index than survival in this category of patients.

Although not all patients dying from prostatic carcinoma necessarily have metastases in bone, it is certainly true of the majority. Bone scanning is the ideal method of assessing new metastases in bone and there are no real problems of interpretation in the progression of M0 to M1 disease (Fig. 1).

Serial scanning in M1 disease may pose prob-

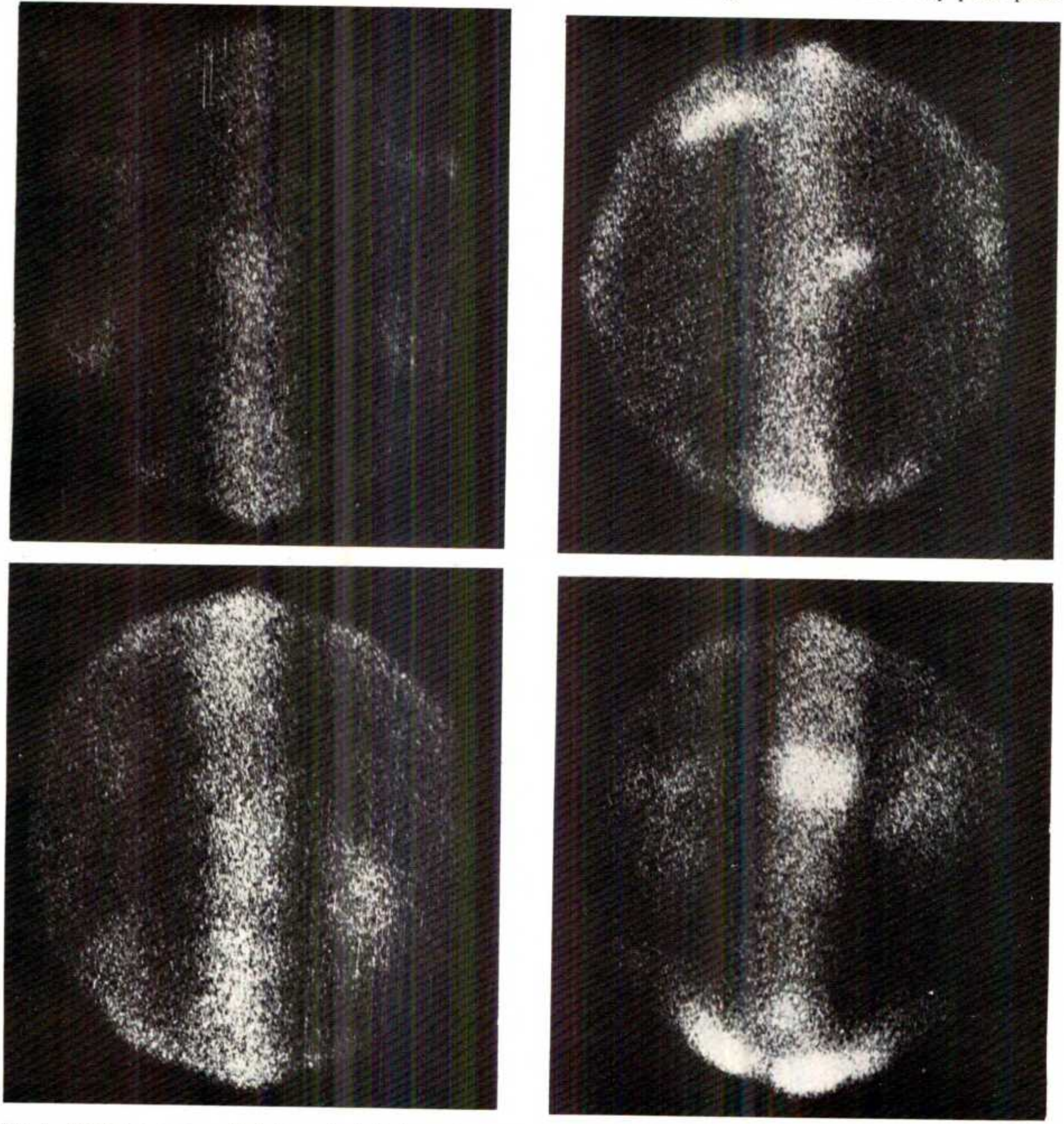

Fig. 1 The bone scans on the left are the initial examination and demonstrate the complete dorsal (top left) and lumbar (bottom left) spine. Those on the right are the dorsolumbar spine of the scan 6 months after starting treatment. Progression from M0 to M1 disease is shown.

lems of quantitation and undoubtedly a computerised facility to assess serial studies would be a real advance. Within the limits of visual assessment one can classify serial scans as showing regression, no change, or progression. In this study, a reduction in the number of "hot spots" or a 50% decrease in their size were the criteria of regression (Fig. 2). The development of new "hot spots" or a 50% increase in the size of existing areas were classified as progression. A relative decrease in density was often seen in association with a favourable clinical response to treatment, but because of difficulty in quantitation was classified as no change.

A favourable response was associated with no change or regression and we are in agreement with Buck *et al.* (1975) that failure of a scan to revert to normal is not evidence of resistance to hormonal therapy. Coupled with this pattern of regression or

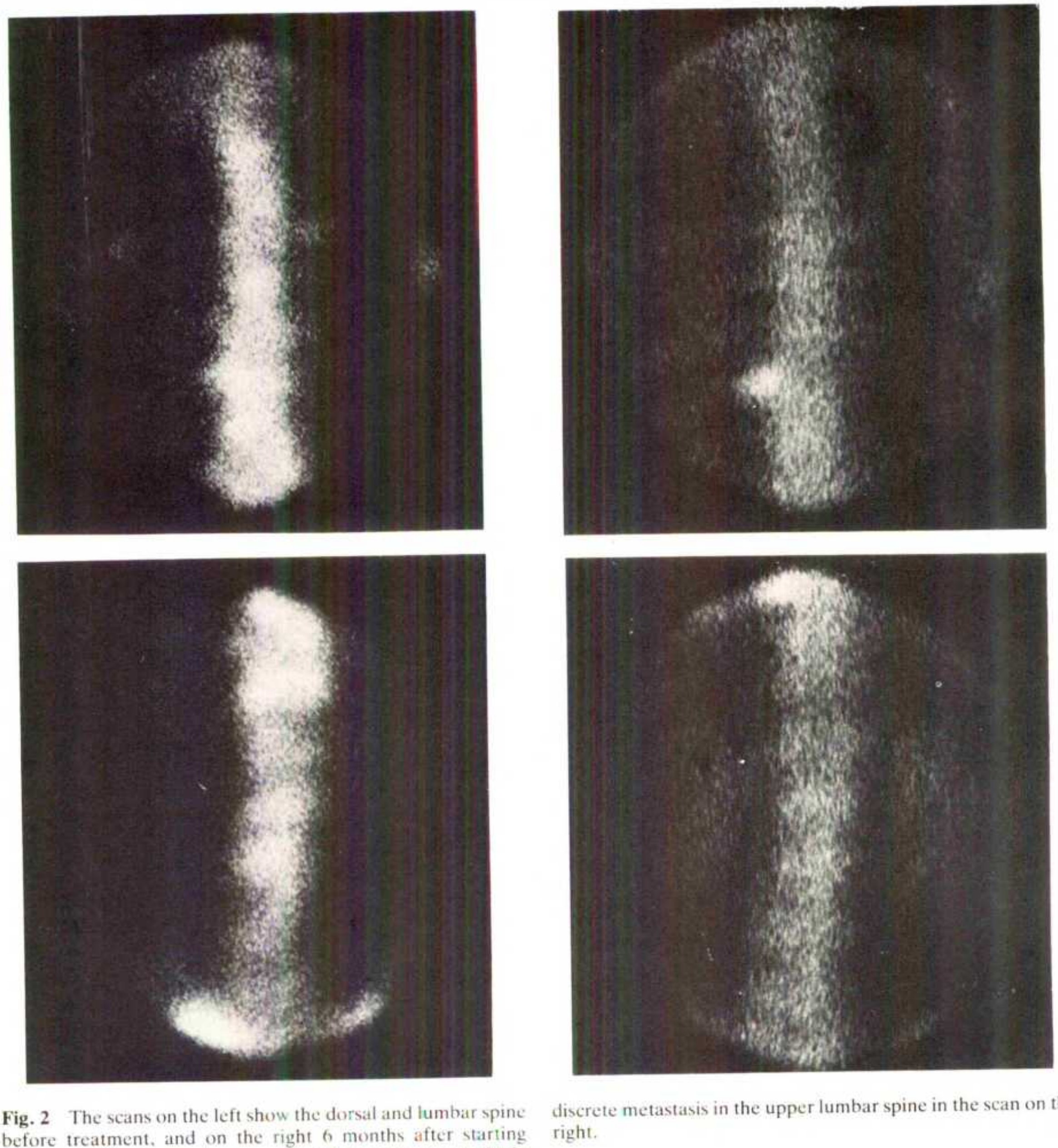

Fig. 2 The scans on the left show the dorsal and lumbar spine before treatment, and on the right 6 months after starting treatment. The "super bone scan" (left) regresses to a single discrete metastasis in the upper lumbar spine in the scan on the right.

no change in scanning was a pattern of increasing sclerosis on serial radiography, which in this situation reflects bone healing (Fig. 3). Serial radiography alone is therefore an unsatisfactory method of assessment as the appearance of new sclerotic areas may be explained either by healing or by the development of new metastases.

Osmond *et al.* (1975) coined the term "super bone scan" to denote diffuse and relatively symmetrical uptake of isotope in the axial skeleton and

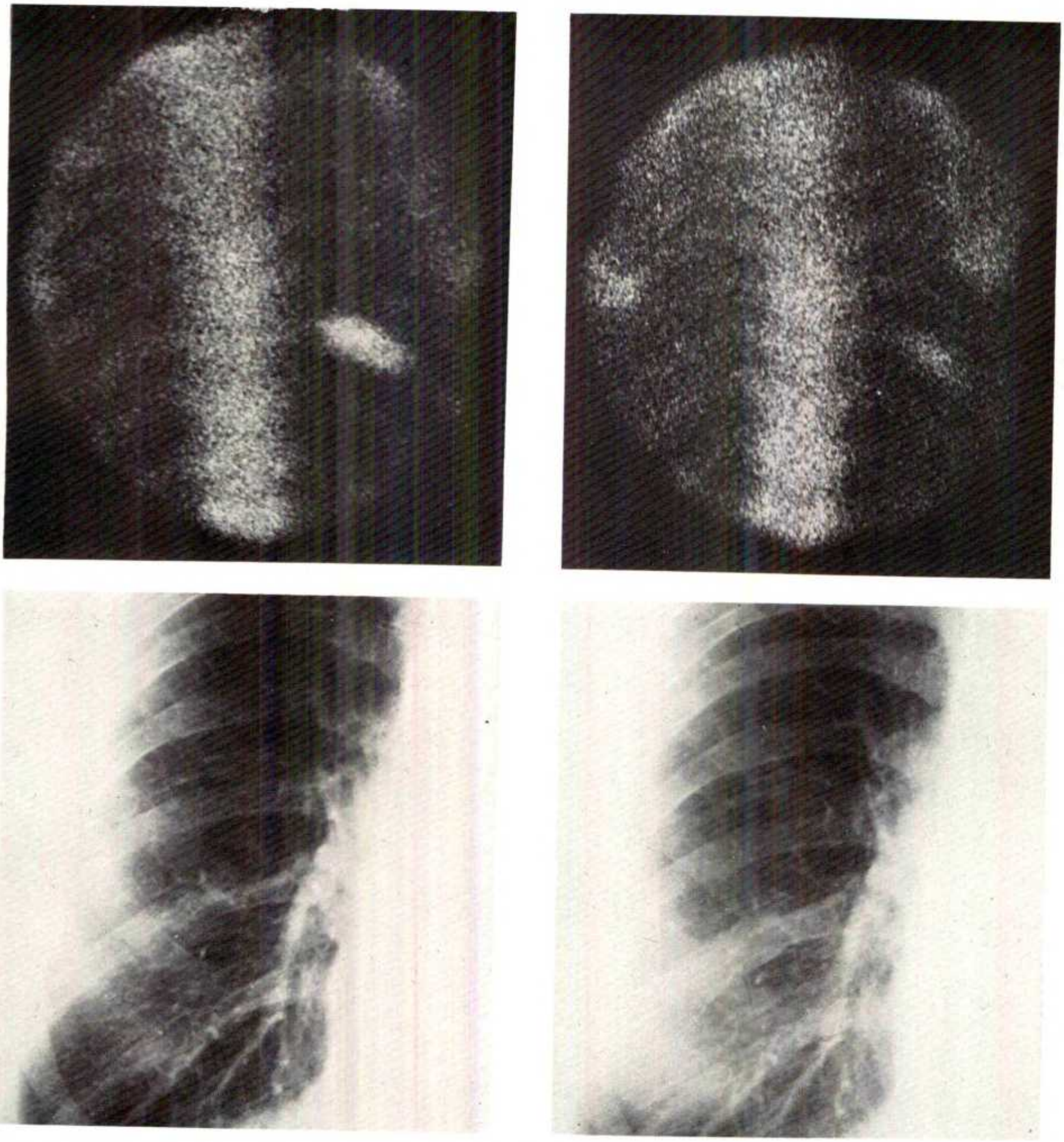

Fig. 3 On the top left is shown the scan of chest and dorsal spine before treatment. Bottom left is an X-ray of the right side of the chest at the same time. On the right are similar examinations performed 6 months after starting treatment. The lytic lesion in the 6th rib becomes sclerotic in the second X-ray, and the "hot spot" decreases both in size and in density in the second scan.

absent or reduced uptake in the kidneys and appendicular skeleton. Apart from the risk of false negative interpretation, this appearance may also be important in serial assessment. The conversion of a "super bone scan" to multiple discrete hot spots seems to represent a favourable response and undoubtedly the converse (Fig. 4) denotes progression.

It is concluded that serial scanning and radiography have considerable value in the follow-up of patients with carcinoma of the prostate. Failure of the scan to revert to normal is not evidence of treatment failure. Serial studies provide early evidence of disease progression but there are many

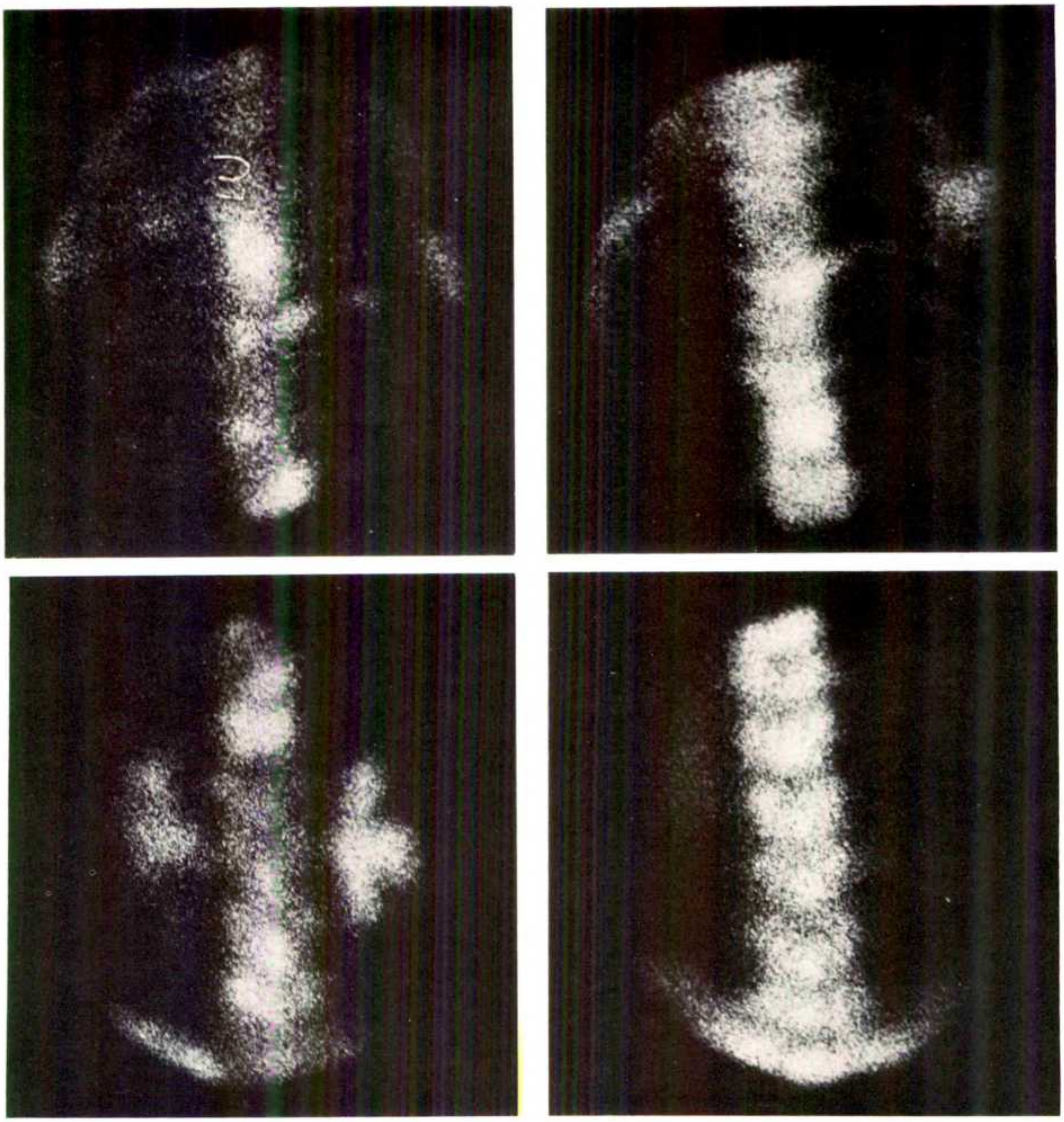

Fig. 4 The scans on the left were taken before treatment and the scans on the right 6 months after starting treatment. The many discrete lesions in the dorsolumbar spine coalesce in the later scan to form a "super bone scan" in which the axial skeleton stands out in bold relief, with absent uptake of the kidneys. This indicates progression.

problems of interpretation. Increasing sclerosis on radiography may denote either healing or the development of new deposits. The "super bone scan" appearance implies diffuse active metastatic disease.

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An Experimental Approach to the Optimum Oestrogen Dosage in Prostatic Carcinoma

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Summary—The action of diethylstilboestrol on the androgen response mechanism of the human prostate has been examined. A simple *in vitro* test system that assesses effects on hormone uptake, receptor binding and translocation to the nucleus has been employed. The test has also been modified to study the effect of diethylstilboestrol on the activity of 5α-reductase, the enzyme responsible for the conversion of testosterone to 5α-dihydrotestosterone. These results are discussed in relation to the dosage of diethylstilboestrol for treatment of carcinoma of the prostate.

Manipulation of the hormonal environment is a common approach to the treatment of carcinoma of the prostate. The most widely used agent is diethylstilboestrol, first synthesised in this Institute by Dodds *et al.* (1938). For some years there has been uncertainty over the optimum dose to use. It has been felt by some authorities that, in addition to the inhibition of the pituitary testicular axis leading to suppression of testosterone production, there may be a local effect of diethylstilboestrol on the prostatic tumour cells (Fergusson, 1958; Susan *et al.*, 1976). This might justify giving patients a higher dose than that required to suppress testosterone secretion (Robinson and Thomas, 1971). In view of the known cardiovascular complications occurring with higher doses of diethylstilboestrol (Byar, 1973) it is important to assess these local effects. We have investigated the *in vitro* action of diethylstilboestrol on the androgen response mechanism of the human benign hyperplastic prostate.

Materials and Methods

Tissue was obtained from retropubic enucleation prostatectomy and was confirmed histologically as benign adenomatous hyperplasia. All experiments were performed on the tissue within 10 min of removal at operation.

Nuclear Uptake of Androgen

This method has already been published in detail (Symes *et al.*, 1978). In brief, 0.5 mm slices of tissue were incubated in Krebs-Ringer bicarbonate buffer containing [^{3}H]-testosterone (1.5×10^{-9}M) and, where appropriate, unlabelled steroids. After incubation for 90 min at 37°C the tissue slices (1.5-2.0 g) were washed and frozen at -70°C. Subsequently the nuclei were prepared and purified from the frozen tissue specimens. The purity of the nuclear preparations was determined by light microscopy and comparison of the optical density at 260 and 280 nm. Any samples that were contaminated with cytoplasm were discarded. Steroids were extracted from the nuclei and the total radioactivity was determined.

Characterisation of Total Nuclear Radioactivity

Where appropriate the total radioactivity was fractionated by paper chromatography in a Bush A system (Bush, 1952). In excess of 80% of the total radioactivity was found in association with testosterone or 5α-dihydrotestosterone in all studies. [^{14}C]-steroids were added prior to extraction of steroids from nuclei and used to correct for procedural losses.

5α-reductase

A crude cytosolic fraction was prepared. Fresh tissue was cut into small pieces and Tris buffer pH 7.0 (0.01M) containing EDTA (5×10^{-5}M), $MgCl_2$ (5×10^{-3}M), β-mercaptoethanol (0.5×10^{-3}M) and NaCl (0.05M) was added (1:5 w/v).

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The tissue was homogenised using a motor driven Silverson homogeniser. The homogenate was centrifuged at 100,000 g for 10 min and the supernatant used as a source of enzyme.

The enzyme was assayed in Tris buffer (see above) containing [^{3}H]-testosterone as substrate, and an NADPH generating system. The optimised assay conditions were as follows: [^{3}H]-testosterone (Sa 100 Ci/mmol) 2.7×10^{-9}M, glucose-6-phosphate 10^{-3}M, glucose-6-phosphate dehydrogenase 10^{-6} g/ml, NADP$^+$ 10^{-4}M, 0.5 ml of 100,000 g supernatant (equivalent to 100 mg of tissue), Tris buffer to 2.5 ml final volume. Incubation was carried out at 37°C for 8 min. The reaction was stopped by the addition of absolute ethanol (2 vols). 50 μg of both authentic testosterone and 5α-dihydrotestosterone and 5×10^3 dpm of [^{14}C]-5α-dihydrotestosterone were added. After removal of ethanol by evaporation, steroids were extracted into chloroform (2×2 vols). The combined extracts were dried and the product 5α-dihydrotestosterone was purified by paper chromatography in a Bush A system. The area corresponding to 5α-dihydrotestosterone was identified by staining a narrow band at the edge of the chromatogram with Zimmerman reagent (0.5% metadinitrobenzene: benzyltrimethyl ammonium hydroxide, 2:1 v/v). The 5α DHT was eluted from the chromatogram, dried, and the radioactivity determined. The [^{14}C] counts were used to correct for procedural losses.

Results

The uptake of radioactivity into the nuclei of prostatic tissue slices *in vitro* has been characterised by us (Symes *et al.*, 1978). At the concentration of [^{3}H]-testosterone employed the system is responding within the linear range and is not fully saturated. While at no concentration could it be demonstrated that diethylstilboestrol inhibited this process, the apparent stimulation that is observed is due to the low affinity of this compound for the mechanism. The affinity is extremely weak as indicated by the comparison to a known anti-androgen, cyproterone acetate, and that of the endogenous hormone (Fig. 1).

Since total radioactivity in the nucleus was not reduced it was still possible that there may have been an alteration in the chemical nature of the radioactive compounds. It has already been demonstrated (Mainwaring *et al.*, 1974) that 17-β-oestradiol has some inhibitory effect on 5α-reductase. In view of the similarity of behaviour of diethylstilboestrol and 17-β-oestradiol a study of the activity of this enzyme was undertaken. Assay conditions were developed based on the procedure of Bruchovsky and Wilson (1968). A crude cytosol was used. Although it is known that 5α-reductase is located in both the microsomal and nuclear fraction the total homogenate contained large fibrous lumps that made reproducible aliquoting difficult. In order to overcome this problem the large particles were discarded in the 100,000 g pellets. Since both the nuclear and microsomal enzyme have similar properties and sufficient activity was associated with the supernatant, this procedure was acceptable. A Km for this enzyme in the region of 10^{-7} to 10^{-8}M was observed (Fig. 2) which is similar to that reported by Bruchovsky and Wilson (1968) for the rat and by Gloyna and Wilson (1969) for the human. Using a concentration of substrate of 2.7×10^{-9}M the effect of diethylstilboestrol and oestradiol was examined. Only at the very highest concentration, 10^{-5}M, could any degree of inhibition be observed (Fig. 3).

To assess the significance of this inhibition on the mechanism the total nuclear radioactivity from slices incubated in [^{3}H]-testosterone and diethylstilboestrol was fractionated. No significant reduction in the relative amounts of 5α-dihydrotestosterone and testosterone in the nuclei could be observed (Table 1).

Discussion

Growth and maintenance of the prostate is known to be dependent on the presence of circulating androgens. The early biochemical events occurring

Table 1 5α-Dihydrotestosterone/Testosterone Ratio

Concentration of diethylstilboestrol in medium	*Experiment 1*	*Experiment 2*
None	2.08	1.55
10^{-7}M	4.78	-
10^{-6}M	1.72	3.02
10^{-5}M	1.06	1.63

Total nuclear counts from incubations in the presence of increasing concentrations of diethylstilboestrol were analysed by paper chromatography. The ratio of counts in 5α-dihydrotestosterone to counts in testosterone is quoted. Counts were corrected for procedural losses; greater than 80% were associated with T and 5α-DHT.

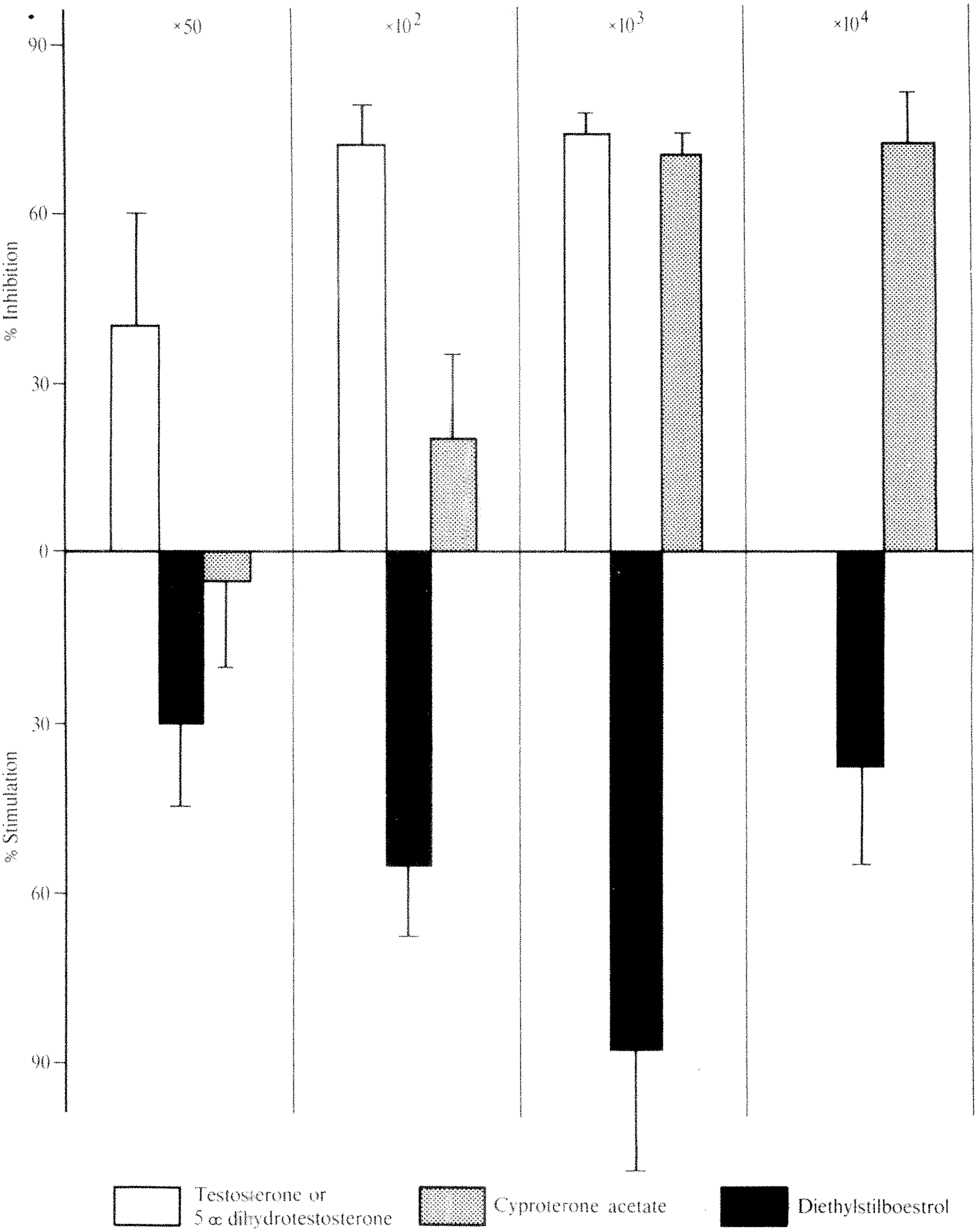

Fig. 1 Competition studies—total nuclear counts were determined from incubations in the presence of $[^3H]$-testosterone and increasing concentrations of cold competitors. SEM indicated. Results expressed as % inhibition or stimulation calculated from:

$$\frac{(\text{cpm/mg DNA}[^3H]\text{-T}) - (\text{cpm/mg DNA}[^3H]\text{-T} + \text{competitor})}{(\text{cpm/mg DNA}[^3H]\text{-T})} \times 100$$

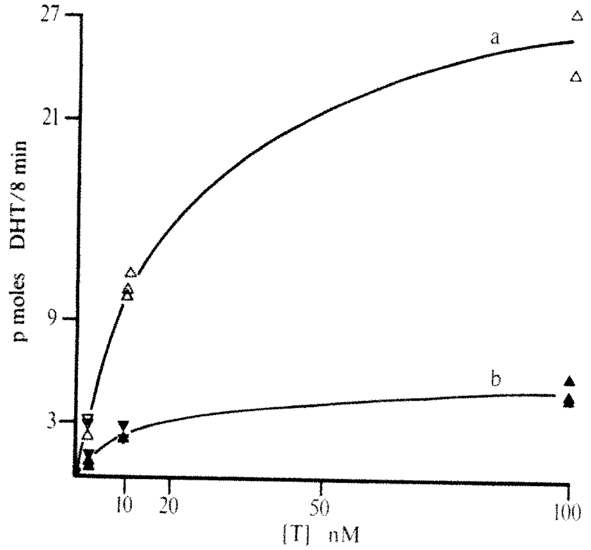

Fig. 2 Determination of 5α-reductase activity: effect of increasing concentration of substrate at 2 different concentrations of enzyme (a) 0.5 ml cytosol (b) 0.1 ml cytosol.

in the tissue are now well established. After uptake the androgen is metabolised rapidly to 5α-dihydrotestosterone which then binds to a cytoplasmic receptor protein; the complex is then modified and translocated to the nucleus. Subsequent steps that are involved with the interaction and expression of the genome are not understood. We have established an *in vitro* test system which encompasses the known stages of the mechanism of action of androgens by studying the nuclear radioactivity of tissue incubated in medium containing [^{3}H]-testosterone. Under the conditions of subsaturation employed in this study diethylstilboestrol results in an increase in nuclear radioactivity levels. This is consistent with its very weak affinity for the androgen receptors (Jung-Testas *et al.*, 1976). This suggests that in the *in vivo* situation the competition is so weak that doses would have to be increased to unacceptable levels to have any inhibitory effect. Where receptors were not fully saturated the lowest dose possible should be selected to avoid stimulation of the nuclear uptake.

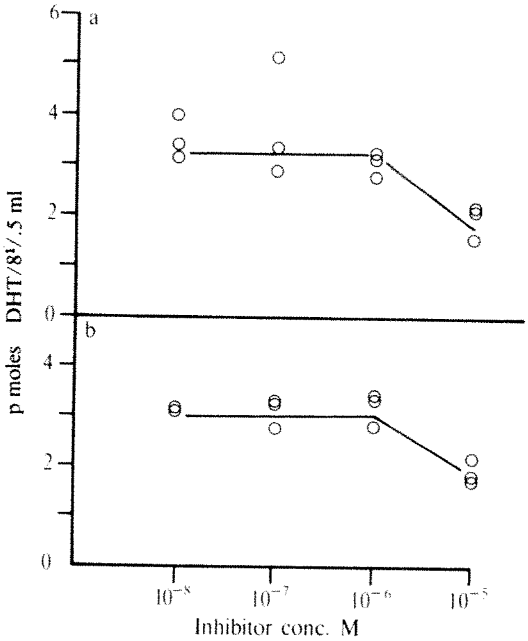

Fig. 3 Determination of 5α-reductase activity: effect of increasing concentrations of (a) diethylstilboestrol (b) 17-β-oestradiol in the presence of 2.7×10^{-7}M substrate and 0.5 ml of cytosol.

Analysis of total nuclear radioactivity demonstrated that no significant changes occurred in the nature of the steroid in the nucleus. This result was confirmed by the independent analysis of the 5α-reductase activity. Although some inhibition (30%) took place the concentration required was extremely high. The normal male oestradiol production rate of 70 μg/day gives rise to plasma levels of 0.5×10^{-9}M (0.15 μg/l). To reach levels of 10^{-5}M would require the administration of at least 2 g/day of diethylstilboestrol, assuming complete absorption and a similar clearance rate. In practice less than 10% of orally administered diethylstilboestrol is absorbed (Fischer *et al.*, 1976). These large doses would be unacceptable because of the inevitable cardiovascular complications and liver toxicity. In conclusion we can demonstrate no effect on the androgen response system that would warrant an increase in the dose over and above that required to suppress testosterone production.

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Receptor Proteins for Androgens in Prostatic Disease*

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Summary—The suitability of an exchange assay with methyltrienolone (R1881) for the measurement of androgen receptors in human prostatic tumours has been investigated. Having established the specificity of this compound for androgen receptor assay, a pilot study was carried out to measure dihydrotestosterone (DHT) receptor in 27 cases of benign hypertrophy and 18 cases of malignant tumour of the prostate.

Androgen dependency of the prostate gland is well established (Ghanadian, 1976) and the presence of a receptor protein which binds dihydrotestosterone in the cytosol has been well documented (Rosen *et al.*, 1975; Ghanadian *et al.*, 1978). Cytoplasmic receptors in target tissues have been considered a prime requisite for the action of steroids. Upon entering the cell, the steroid binds to cytoplasmic receptor to form the steroid receptor complex, then translocates into the nucleus and binds to acceptor sites in the chromatin materials. This interaction eventually leads to protein synthesis and cell division (O'Malley and Schrader, 1976).

The assay of cytoplasmic receptors for the assessment of tumour response to endocrine therapy has been used by several investigators. In breast tumours there is now good evidence to suggest that the responsiveness of these tumours to hormonal manipulation can be evaluated by the measurement of oestrogen and progesterone receptors (Jensen, 1977). In prostatic cancer, several groups have embarked upon a similar programme in order to assess the potential use of cytoplasmic receptors in the prediction of hormonal responsiveness. Early attempts to quantify androgen receptors in the human prostate were not successful. This was due mainly to the presence of sex hormone binding globulin (SHBG) in the cytosol as well as the limited number of receptor sites available to bind ^{3}H DHT (Steins *et al.*, 1974; Mobbs *et al.*, 1975). With the introduction of the synthetic androgen methyltrienolone (R1881), which has a high affinity for DHT receptors and does not bind to SHBG or undergo metabolism (Bonne and Raynaud, 1975), it was possible to develop a suitable technique for the measurement of free and total cystoplasmic androgen receptors in the human prostate (Ghanadian *et al.*, 1978).

In this report we describe further investigations into the specificity and suitability of R1881 for DHT receptor assay and present a preliminary study on receptor levels in benign and malignant tumours.

Materials and Methods

Prostatic tissue was obtained from 27 patients with benign prostatic hypertrophy (BPH) undergoing retropubic prostatectomy and 18 patients with carcinoma of the prostate treated by transurethral resection. Ten patients with carcinoma had received no treatment and 8 had been treated with either oestrogens, oestrogen and orchiectomy or cyproterone acetate. Tissue was either transferred to a container and placed in crushed ice ready for immediate use, or frozen in liquid nitrogen and stored at −70°C for later use.

Steroids

5α-dihydrotestosterone (DHT), progesterone and cortisol were supplied by Sigma Chemicals; a solution of 10 nmol/ml of each was prepared in absolute ethanol.

(1,2,6,7-^{3}H) progesterone (specific activity 87 Ci/mmol) and (1,2,6,7-^{3}H) dihydrotestosterone (specific activity 114 Ci/mmol) were supplied by Radiochemical Centre, Amersham. Stock solutions of 50 pmol/ml of methanol were used.

Methyltrienolone (17β-hydroxy-17α-methyl-estra-4,9,11-triene-3-one) (R1881) was kindly donated by Roussel Uclaf. A stock solution of

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50 pmol/ml of (^{3}H)R1881 (specific activity 58.2 Ci/mmol) was prepared in a solution of toluene:methanol (9:1). Radioinert R1881 (10 nmol/ml) was prepared in ethanol. All solutions were stored at 4°C. Buffers, solvents and scintillation fluids were prepared as described previously (Ghanadian *et al.*, 1978).

Preparation of Cytosol

Cytosol was prepared as previously described (Ghanadian *et al.*, 1978). In the case of frozen tissue, homogenisation was performed in a microdismembrator (Scientific Instruments Ltd). The resulting powdered tissue was suspended in 3 vol of buffer and in order to ensure a homogeneous suspension, the mixture was re-homogenised with a Teflon homogeniser. The homogenate was used for the preparation of the cytosol.

Specificity Study

In order to substantiate our previous data on the specificity of R1881 binding to the DHT receptor, the following experiments were performed. Aliquots of the cytosol prepared from BPH tissue were equilibrated with an equal volume of 1 mg/ml solution of protamine sulphate (Sigma Chemicals) at 0°C for 15 min. This was followed by centrifugation for 10 min at 800 g at 4°C. The resulting precipitates were washed 6 times with ice cold Tris EDTA buffer and incubated at 0°C for 16 h with solutions of 5 nM of either ^{3}H R1881, ^{3}HDHT or ^{3}H progesterone in the presence and absence of 100-fold excess of radioinert R1881, DHT and progesterone. All incubations were carried out with Tris EDTA buffer containing 10% (v/v) glycerol. Following incubation, the tubes were centrifuged and the supernatant decanted. The resulting precipitates were washed 6 times with buffer and finally the radioactivity was extracted from the precipitates with ethanol (2×0.5 ml). The ethanolic extracts were dried in glass scintillation vials prior to the addition of scintillation fluid. The radioactivity was counted in a scintillation spectrometer.

Table 1 Specificity of DHT Receptor for DHT, R1881 and Progesterone Using Protamine Sulphate Precipitation Technique

Tritiated steroid (5 nM)	*Competitor (500 nM)*	*Competition (%)*
^{3}H R1881	-	-
	R1881	92
	progesterone	83
	DHT	79
^{3}H DHT	-	-
	R1881	61
	progesterone	50
	DHT	70
^{3}H progesterone	-	-
	R1881	15
	progesterone	10
	DHT	9

Measurement of Free and Total Cytoplasmic DHT Receptor

The procedure for measurement and analysis of the results has been reported previously (Ghanadian *et al.*, 1978).

Results

Specificity Study

The results showed that R1881, progesterone and DHT are strong competitors for the binding of ^{3}H R1881 and ^{3}H DHT. However, when the precipitates were incubated with ^{3}H progesterone, negligible competition for the 3 tested steroids was observed (Table 1).

Cytoplasmic DHT Receptor in Benign Prostatic Hypertrophy

The concentration of total DHT receptor was measured in 27 samples of BPH. The mean ±SEM for the total binding sites was 90.61±8.50 (fmol/mg protein). The range varied between 30.7 and 218 fmol/mg protein. In 14 samples of BPH the mean ±SEM for the free receptor was 6.88±0.75 (fmol/mg protein). The range was between 3.3 and 11.7 (fmol/mg protein).

Cytoplasmic DHT Receptor in Carcinoma of the Prostate

DHT receptor was measured in 18 patients with carcinoma of the prostate. The results are shown in Table 2.

Discussion

The present study confirms our previous report on the use of an exchange assay with tritiated methyltrienolone for the measurement of dihydrotestosterone receptors in prostatic tumours (Ghanadian *et al.*, 1978). The additional studies on the specificity of R1881 have supported our

Table 2 Concentration of Total, Free and Bound Cytoplasmic DHT Receptor in Carcinoma of the Prostate. (Range in brackets)

	Concentration (fmol receptor/mg protein)		
	Total	*Free*	*Bound*
Untreated (10)	148.0±51.0 (52.0−525.0)	4.3±0.7 (1.7−9.2)	142.2±51.2 (32.8−520.5)
Treated (7) oestrogen, orchiectomy and cyproterone acetate	119.1±59.4 (17.5−466.0)	9.3±2.8 (1.5−21.4)	109.8±60.3 (2.6−461.0)
Treated (1) oestrogen	N.D.	N.D.	N.D.

N.D. = none detected.

view that under these experimental conditions there is no evidence for the presence of progesterone receptors. The specificity results following precipitation by protamine sulphate have clearly demonstrated that progesterone competes equally well with the specific binding of either dihydrotestosterone or R1881. This, together with the well known ability of progestogens to bind androgen receptors (Horwitz *et al.*, 1975), suggests that the claims for the presence of "progesterone receptor" or "progesterone binding component" (Asselin *et al.*, 1976), based on competition experiments, are unfounded.

The present method provides optimum conditions for the measurement of the total receptor population as well as free receptors and allows a proper evaluation of the changes in the bound/free ratio following any endocrine manipulation of the tumour.

In this study, DHT receptors were measured in 18 malignant tumours, 8 cases of which were treated with either oestrogens, oestrogen and orchiectomy or cyproterone acetate. Although the results show an increase in the concentration of the *free* receptors in the treated malignant patients, no conclusion can be drawn from these limited numbers.

There was a wide variation in the total number of binding sites both for benign hypertrophied and malignant prostates. The mean value for the concentration of total receptor sites in untreated cancer patients was higher than that in benign specimens. However, there was considerable overlapping for individual cases from each group and it is possible that this is due to the presence of a significant proportion of benign tissue in the malignant specimen. It would be advisable in future receptor assays to quantify the proportion of non-malignant cells for each case.

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Late Results of Skin Inlay Urethroplasty

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Summary—Sixty-two patients undergoing either one-stage or two-stage skin inlay urethroplasty for stricture of the urethra have been reviewed. The success rate and incidence of complications are discussed. The technique of skin inlay urethroplasty requires a considerable degree of surgical expertise and a similar skill in clinical evaluation is required in the selection of patients for this procedure.

Urethral stricture is one of the oldest problems known to urology. Urethral dilatation is a simple and, in many cases, most effective treatment. However, dilatation may become a tedious procedure for both urologist and patient, and for this reason much effort has been directed towards alternative surgical procedures to produce a permanent cure of the stricture. Skin inlay urethroplasty is not a new operation, but its popularity amongst urologists was established by improved techniques as described first by Johanson (1953) and later Turner-Warwick (1960), and Blandy *et al.* (1968). These initial two-stage operations were complemented subsequently by one-stage repair techniques using an island flap as described by Orandi (1968) and in a modified form by Blandy and Singh (1975). The interest aroused by the description of these techniques and the encouraging results reported from these procedures (Blandy *et al.*, 1971, Orandi, 1972; Ashken, 1974) prompted an increase in the number of skin inlay urethroplasties performed in the Bristol and Bath areas. A retrospective study, however, shows a steady decline in the number of operations after this period of initial enthusiasm. In the last 12 months only 2 skin inlay procedures have been performed. This paper sets out to assess possible reasons for the decline in the use of skin inlay urethroplasty in the treatment of urethral stricture.

Patients and Methods

A total of 62 patients undergoing skin inlay urethroplasty between 1965 and 1976 has been studied (Fig. 1). The age of the patients ranged from 13 to 78 years (Fig. 2). The aetiology of the strictures shows a typical distribution (Table 1). The site of

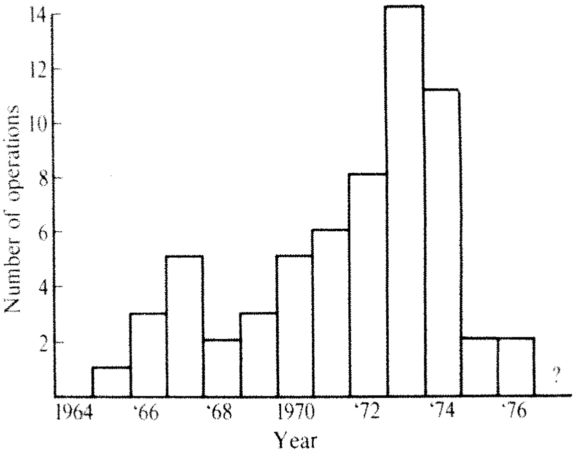

Fig. 1 Skin-inlay urethroplasty in 62 patients: Year of operation

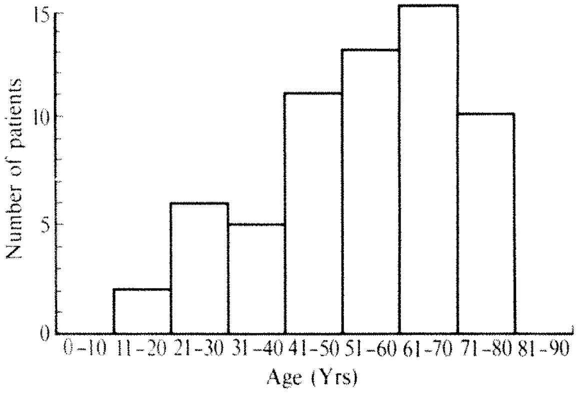

Fig. 2 Skin-inlay urethroplasty in 62 patients: Age at operation

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Table 1 Aetiology of Stricture

Congenital	6
Inflammatory	10
Traumatic	
a. Fractured pelvis	8
b. Soft tissue injury	2
Post-operative	
a. Transurethral prostatectomy	15
b. Open prostatectomy	2
c. Urethral instrumentation (Catheter or cystoscope)	5
Post radiotherapy	1
Not stated	13
Total	62

the stricture, including 6 patients with 2 strictures, is shown in Table 2. Seventeen of the patients had a skin inlay urethroplasty as the primary treatment of their stricture and in the remaining 45 regular dilatation had been employed. The period of the patients' lifetime over which dilatation had been used is shown in Fig. 3. Whilst in the majority of patients this was of less than 5 years' duration there were 4 patients in whom urethral dilatation had been performed for over 25 years – 1 patient having been dilated at fortnightly intervals for 50 years.

Table 2 Site of Stricture

Meatus	1
Anterior urethra	12
Bulb	34
Membranous urethra	20
Prostatic urethra	1
Total	68*

*6 patients had double stricture

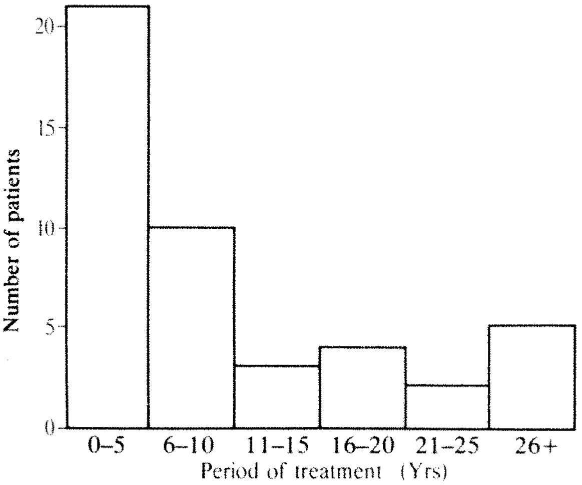

Fig. 3 Skin-inlay urethroplasty in 45 patients: Period of treatment by urethral dilatation

The indications for the operation are shown in Table 3. In 10 patients surgery was the initial treatment. In another 7 dilatation was attempted but abandoned after only 1 or 2 attempts. In the remainder, urethroplasty was undertaken at a later stage in the majority as an alternative to a painful, difficult, or too frequent dilatation. Two patients had minimal urinary problems but could not ejaculate adequately because of their stricture. In 2 patients recurrent perineal sepsis, and in 4 patients chronic post-infective perineal fistulae, were complicating the stricture. One patient who required regular check cystoscopy for bladder tumour had mild urinary symptoms but needed dilatation before these endoscopic examinations. In 5 patients the stricture was producing bladder outflow obstruction of a significant degree, both in terms of changes in the upper urinary tract and in symptoms.

Table 3 Indications for Operation

Initial treatment	10
Painful dilatation	4
Difficult dilatation	25
Frequent dilatation	8
Urethral fistula	4
Outflow obstruction	5
Ejaculatory problem	2
Recurrent sepsis	2
Recurrent cystoscopy	1
Not stated	1
Total	62

The operations, either one-stage or two-stage, were carried out by surgeons of varying experience in this type of operation and who on occasions may not have kept rigidly to the original operative descriptions – hence the inverted commas (Table 4). Eleven patients, having undergone the first stage of a two-stage procedure, declined to have further surgery and were left with a permanent perineal urethrostomy. These have been included in the one-stage group.

Results

The results in 58 patients are shown in Table 5.

Table 4 Operative Procedures

One-stage	
a. "Blandy"	16
b. "Orandi"	15
c. Other	1
d. "Failed" Two-stage	11
Two-stage	
a. "Johanson"	8
b. "Turner-Warwick"	12
Total	63*

*(Includes one patient with 2 procedures)

Table 5 Results of Stricture Treatment

62 Patients	
Cured	35
Better	13
Failed	8
Worse	1
Not known	1
Total	58

Dead – 4
- a. "Heart failure" post-op.
- b. Coronary thrombosis @ 3 months
- c. Carcinoma of bladder @ 2 years
- d. Cerebral haemorrage @ 2 years

Thirty-five have no residual stricture; 13 continue to require dilatation, but much less frequently. In 8 patients the stricture was not eliminated, and in 1 it was worse. Follow-up varies from 18 months to 8 years (mean 3.7 years).

Four patients are dead. One developed heart failure in the immediate post-operative period, almost certainly due to a coronary thrombosis, and another died with the same complaint 3 months after urethroplasty.

Complications are shown in Table 6. Wound infection, urinary sepsis and the one case of bacteraemic shock all responded to antibiotics. Hair ball occurred 6 times but 1 patient had no less than 3 recurrences of this condition. One patient developed a collection of calculi at the site of the urethroplasty. These, and the hair balls, were all removed surgically. Two patients had secondary haemorrhage and 1 a deep vein thrombosis – all responded to routine treatment. Two patients complained of scrotal sensation when passing urine and 2 patients had failure of ejaculation due to pooling of semen in the repaired urethra. In 1 of these patients there was a diverticulum at the site of the skin inlay.

Table 6 Complications of Operation

Wound infection	7
Fistula formation	14
Diverticulum formation	11
Hair ball	6
Urethral calculus	1
Bacteraemic shock	1
Urinary sepsis	5
Haemorrhage	2
Scrotal sensation	2
Ejaculatory impotence	2
Deep vein thrombosis	1
Incontinence	9
Restenosis	23

Diverticulum formation occurred in 11 patients. As well as the problems of ejaculation the presence of this diverticulum can also result in post-micturition dribbling due to passive drainage of urine from the urethra after the completion of active micturition. This occurred in 6 patients: 3 have had the diverticulum excised, a relatively simple procedure; 3 control this post-micturition dribbling by digital expression of the urine from the diverticulum at the end of micturition. Five patients with a definite diverticulum on urethrography have no associated symptoms.

Fistula formation occurred in 14 patients, in 2 cases associated with the second stage of a two-stage procedure, and in 12 with a single-stage skin inlay procedure. In 9 cases the fistula closed spontaneously within a few weeks. In 3 cases surgical closure was undertaken with success. One patient has a persistent fistula but refused further treatment as it caused him minimal difficulty. Another patient had intermittent drainage through his fistula, and again was not sufficiently bothered by it to want further surgery. In this last patient the fistula was associated with restenosis and not surprisingly the fistula closed spontaneously after dilatation, only to reappear as the stricture reformed.

Restenosis occurred in 23 cases. Six of these followed the first stage of a two-stage repair necessitating a revision of the perineal urethrostomy. Sixteen patients required regular dilatation of varying frequency and difficulty. One patient had a meatoplasty and 3 had intermittent Otis urethrotomy. One patient had a Sachse optical urethrotomy. Though the complication of restonosis is highly significant in the assessment of the success or failure of this operation, there remains one further complication which is a source of grave concern – the problem of urinary incontinence.

Nine patients were incontinent after surgery. One had been rendered incontinent by the same prostatectomy that gave him his stricture, and urethroplasty enabled his incontinence to be managed more easily. Another had known sphincter damage following spinal trauma and was also incontinent before operation; cure of his stricture was associated with a marked improvement in his continence and though still troubled by the stress leakage in the day, he became dry at night. One patient had a contracted bladder following radiotherapy for carcinoma of bladder; cure of his stricture resulted in both stress and urge incontinence, though again he was dry by night. One patient developed incontinence post-operatively but this was associated with marked progression of his Parkinson's disease and it was felt that this, rather than the urethroplasty, was contributing to the incontinence. The remaining 5 patients who became incontinent following urethroplasty had all undergone prostatectomy. One patient had had a simultaneous prostatectomy and urethroplasty, and in 4 the stricture had resulted from a previous prostatectomy.

Discussion

In this series of 62 patients with skin inlay urethroplasty both the failure rate and incidence of complications are higher than in other reported series (Ashken, 1973; Orandi, 1974; Blandy *et al.*, 1975). This may reflect the differing surgical experience of the surgeons involved in the operation, and it could be significant that the best results have been achieved by the one author (JBMR) who has the largest personal series in this group. A further important consideration is that the urethroplasty procedures during the period under review were almost exclusively of the skin inlay type, there being no patch graft or direct anastomosis procedures performed. In some cases, use of these alternative techniques might have reduced the morbidity and improved the results. It would seem that in the selection of patients and in the perfection of surgical technique, increasing experience improved the results of skin inlay urethroplasty.

Unlike the reports from other authors (Blandy *et al.*, 1971) there was a definite incidence of post-operative incontinence in those patients who had undergone prostatectomy. However, it should be said that there was a total of 19 patients who had undergone prostatectomy prior to their urethroplasty and in whom all but 2 related their posterior urethral stricture to their operations (see Table 1). Five of these, including one who had a simultaneous prostatectomy, became incontinent following the operation. As has been discussed by Blandy (1976), the precise mechanisms for control of continence after urethroplasty on patients with previous prostatectomy are not clear. Though in some ways it is interesting to speculate as to why the remaining 14 patients are continent, it does seem necessary from these results to consider the possibility of incontinence after skin inlay urethroplasty for strictures in the region of the external sphincter in this group of patients.

The formation of post-operative fistulae and urethral diverticula after urethroplasty was not a serious complication. They either required no treatment, *i.e.* they were symptomless and resolved spontaneously, or they were cured by simple and in every case successful minor surgery.

Hair ball and stone formation were impressive and distressing complications which again were easily treated by endoscopic or surgical removal. The problem of recurrence was exemplified by the one patient who had 3 further hair balls over a 2-year period. In the early cases attempts were made at depilation but in later cases this was not done. The provision of a sterile urine with an adequate flow and absent urethral pooling seems to be the best way to eliminate this problem.

The complication rate was high in this series, and as a result a wide range of secondary surgical procedures was required. This additional surgery

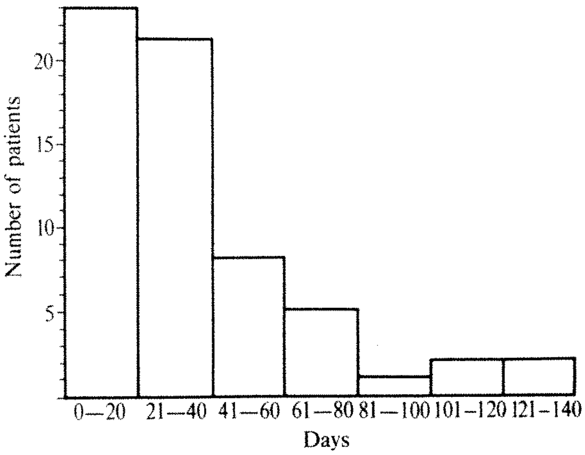

Fig. 4 Skin-inlay urethroplasty in 62 patients: Duration of hospital stay

inevitably required longer in-patient stays and overall these patients spent a considerable period of time in hospital (Fig. 4).

Skin inlay urethroplasty is an operation that can cure urethral stricture and thus save the patient from both the symptoms of the stricture and the problems of difficult or painful dilatation. It does, however, as in this series, have a significant level of complications and an absolute failure rate of 15%. Two patients died following the operation though not due to any specific complication of the urethroplasty. Skin inlay urethroplasty should be seen as one of several alternative treatments to urethral dilatation in the management of stricture. Urethral dilatation itself still remains an acceptable treatment for many patients and the possible complications of skin inlay urethroplasty should be carefully considered before recommending any change in management.

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The One-stage Island Patch Urethroplasty

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Summary—Dartos-pedicled scrotal skin island patch urethroplasties were performed in 72 patients and followed up for up to 7 years. Restenosis was seen at the site of the stricture in 5 cases and one developed a new meatal stenosis. There were no deaths. Hair-stones occurred in 4 patients and were removed endoscopically. One too-large pouch was trimmed. No patient was incontinent. More than one patch may be used for long or multiple strictures.

If the plane of cleavage between dartos and skin is opened a pedicle can be fashioned for a patch of scrotal skin which can be adapted to almost any urethral stricture and so permit a scrotal inlay urethroplasty to be performed in a single stage (Leadbetter and Leadbetter, 1962; Orandi, 1972; Blandy and Singh, 1975). Over the last 7 years this island patch technique has been used more and more often. In each case it has been necessary to weigh the benefits of a one-stage operation against the disadvantage of being unable to adjust the skin inlay between the first and second stages. Furthermore, over the same period of time, other alternative methods of dealing with urethral strictures have been canvassed. Among these the use of free skin grafts (Devine *et al.*, 1976), excision and end-to-end anastomosis (Azoury and Freiha, 1976) and a return to internal urethrotomy under vision (Lipsky and Hubmer, 1977) have all been advocated. We report our experience and results using the island patch urethroplasty.

Patients and Methods

Seventy-two men with urethral stricture were operated upon by 5 surgeons at the London and St Peter's Hospitals from 1971 to 1978, and all followed-up either in person or by questionnaire. Thirty-nine cases have been followed for more than 2 years. The strictures were of varying aetiology (Table 1) and were located in every part of the urethra (Table 2), extending its full length in 4 cases. At first our use of this type of urethroplasty was restricted to strictures which were short, accessible and uncomplicated by false passages or fistulae. With increasing experience it was learned that the patches could be adapted to more and more long and difficult strictures. They could be taken from the tip of a ∩-shaped flap raised as in the usual scrotal-flap urethroplasty (Blandy *et al.*, 1968), so leaving the decision as to whether to do the operation in 1 or 2 stages until the stricture had been laid open, and could be made from almost any part of the scrotum and via almost any incision. It was possible to make use of more than one patch, if the stricture seemed to require this, and on occasion the patch could be rolled up into a complete tube and used to replace a length of urethra resected for tumour, as was done in 2 cases not included in this series.

Table 1 Aetiology of Stricture in 72 Island Patch Urethroplasties

Congenital	13	18%
Traumatic, iatrogenic	18	25%
accidental	17	24%
Inflammatory (gonococcal)	15	21%
Passing stone *per urethram*	1	1%
Unknown	8	11%
Total	72	100%

Initially many of the patches were made some-

Table 2 Site of Stricture in 72 Island Patch Urethroplasties

Penile urethra	14	19%
Post-traumatic; membranous	9	12%
Bulbar	45	63%
Full length or multiple	4	6%
Total	72	100%

Read at the 34th Annual Meeting of the British Association of Urological Surgeons in Brighton, June 1978.

Table 3 Early Complications in 72 Island Patch Urethroplasties

Urinary infection	18	25%
Fistula (temporary 7)	0	0%
Wound infection	1	1%
Haematoma (returned to theatre, 2)	6	8%
Necrosis of skin edge	3	4%

what too large, and a pouch was seen in the post-operative urethrogram. Latterly we have made efforts to get the skin patch the right size, and have adapted the tinfoil template used by Devine *et al.* (1976) in their free skin grafts. At first we used a continuous 3/0 chromic catgut suture but now find interrupted stitches more satisfactory. At first a suprapubic cystostomy was used in all cases to protect the patch; today we use a narrow indwelling catheter no more than 14 FG in calibre.

Results

There were no operative deaths. Urinary infection, sometimes with evidence of bacteraemia, was seen in 18 cases (25%) (Table 3). A temporary leak of urine occurred in 7 cases, but was never permanent and no fistulae had to be excised later on. Wound sepsis occurred in one patient, and responded to the appropriate antibiotics. Wound haematoma occurred in 6 cases (8.3%) though it has been minimised in recent years since we have routinely put on a plastic-foam pressure dressing under a T-bandage. In 2 of these patients it was necessary to return them to the operating theatre and evacuate the haematoma. In the first of these the patch was intact, but it was thought safer to evacuate the haematoma and pack the perineal wound. The incision healed with a linear scar and the patch never leaked. In the second patient, when the haematoma was evacuated the patch was found to have come undone but was obviously viable. It was sutured back in place and there was no further trouble. (On this second occasion interrupted sutures were used, and have been used ever since.)

Late results (Table 4)

Table 4 Late Complications of 72 Island Patch Urethroplasties

Restenosis (dilated 4, new patch 1, meatoplasty 1)	6	8%
Hairball-calculi, removed endoscopically	4	6%
Need to express urine after voiding	17	24%
Pouch seen in urethrogram (8 in 28 urethrograms)	8	29%
Persistent pyuria or urinary infection	8	11%
Impotence (?)	1	1%
Incontinence	0	0%

No doubt the full catalogue of late complications remains to be compiled; nevertheless, in a follow-up extending for up to 7 years the most important problem must be restenosis which occurred in 6 cases (8.3%). In one this was due to a new stricture at the meatus: in the remaining 5 it was due to a circular narrowing at the proximal end of the patch, suggesting that the incision of the original stricture had been incomplete. Regular infrequent dilatation keeps 4 of these patients comfortable: another patch was put into the fifth and the patient with a meatal stricture was treated by meatoplasty.

Stones formed on the hairs of the skin patch in 4 patients (5.5%) and in all cases were removed endoscopically. It has been our impression that stones form only when the pouch has been made too big. Such a pouch was noted in 8 of the 28 patients who underwent urethrography during the follow-up period, while 17 patients replied to a questionnaire that they had to milk urine and semen by digital pressure along the urethra after voiding or ejaculation.

In 8 patients persistent pyuria had been taken as an indication for long-term antibiotic medication by their general practitioner, though it seems more probable that the cells were from the skin epithelium.

Impotence was specifically discussed in the follow-up. Only 2 patients were impotent after this form of urethroplasty: the first had been impotent since his fractured pelvis: the second complained more that his prowess was diminished and less remarkable than that it was absent, and we have formed the view that he is not a satisfactory witness.

None of these patients is incontinent, even though the skin patch was used to bridge a gap in the membranous urethra in 7 cases, and was placed high in the bulbar urethra in a further 47. This finding is in accord with previous studies on continence after skin inlay urethroplasties (Edwards *et al.*, 1972; Colapinto and McCallum, 1976).

Discussion

A one-stage urethroplasty has many advantages over a 2-stage procedure, and the island patch on its dartos pedicle seems to have certain advantages over alternative one-stage techniques. Almost any urethral defect can be bridged without risking post-operative shortening of the urethra and consequent chordee. Where there are 2 or 3 strictures one may use 2 or 3 patches.

The chief drawback is the lack of opportunity to adjust or revise the scrotal skin inlay between one stage and the next. As these results show, this was a disadvantage in 5 patients in this series (7%), but not a grave one. We have learned to take great care to make sure that the stricture is fully divided before putting in a patch.

Although much has been said and written about the evil consequences of putting hair-bearing skin into the urethra, we saw such consequences in only 4 cases (5.5%) despite making no effort to effect epilation. Study of the urethrograms in these patients always shows that the pouches had been made rather too big and baggy in the first place and that stones are more likely to be avoided by taking trouble to get the patch the right size than by attempting electrolytic epilation which, in any event, is seldom complete however hard one tries. Since the small stones seen in these cases have been easy to deal with endoscopically, first cutting the hairs with endoscopic scissors and then extracting the calculi with biopsy forceps, we have reason to feel that this hazard has been somewhat exaggerated. Only in one case was it also thought necessary to trim away a surplus patch, and this too is a quick and easy operation.

The question must be answered, whether there is any need to go to all the extra trouble to provide the skin patch with its own blood supply in its dartos pedicle, when others claim good results with free full-thickness skin grafts. In our 2 patients who developed a post-operative haematoma, each patch remained perfectly viable, even though in one case it came away from the urethral defect completely. We doubt whether free skin grafts could have survived such an insult.

In summary, the dartos-pedicled scrotal skin island patch urethroplasty can be recommended as a versatile and technically simple solution to the majority of urethral strictures, and appears to be successful in more than 90% of cases.

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Urethral Injury and Fractured Pelvis

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Summary—In 333 consecutive cases of fractures of the pelvis admitted as emergencies to one hospital 53% were in males, of whom 34 had suspicious clinical signs of urethral or vesical injury.

In 15 patients catheterisation was performed uneventfully and in no case did this make the injury worse; in 8 an attempt at primary realignment was performed, resulting in 4 cases without any stricture, and 2 who needed annual dilatation only. In 4 additional cases associated laceration of the bladder was repaired of which one had no stricture and 2 needed infrequent dilatations. In a further 41 cases a catheter was used and led to no strictures.

Among 67 males with post-traumatic urethral injuries caused by pelvic fracture the best results were seen when the 2 ends were approximated. In 4 cases a stricture was prevented entirely, and in 17 others it led to an easy urethroplasty. Difficult strictures occurred in severe injuries with uncorrected displacement of the soft parts. Where feasible, early surgical repair appears to give the best chance of minimising the severity of subsequent urethral stricture.

When injury to the urethra is suspected in a patient with a fractured pelvis, there is still some uncertainty as to how best the case should be managed so as to avoid, or at least minimise, subsequent urethral stricture. Authorities argue that the passage of a catheter may turn an incomplete urethral rupture into a complete one, and a simple pelvic fracture into a compound one; that the torn ends of the urethra will come together as the haematoma resolves and the consequent stricture may be cured by means of a urethroplasty, which will avoid impotence (Morehouse *et al.*, 1972; Mitchell, 1975; Coffield and Weems, 1977). Against this are the views of those who believe that the torn ends of the urethra should, whenever possible, be brought together so that the resulting stricture should be as short as possible, and sometimes avoided altogether (Jackson and Williams, 1974; Blandy, 1975; Malek *et al.*, 1977). According to these investigators little harm arises in cases of doubt by the gentle passage of a narrow soft catheter.

We have examined a series of patients with fractured pelvis and another series of patients treated for urethral stricture in order to see how the early management of the injury had affected the subsequent stricture. In both series we were particularly interested to see what harm catheterisation had caused and whether early attempted surgical repair of the ruptured urethra had made things worse.

Patients

Cases of Fractured Pelvis

A consecutive series of 333 emergency admissions for fractured pelvis to the London Hospital from 1950 to 1978 was studied; 176 were male and 157 were female. Although injury to the urinary tract was present in a proportion of these females, they present different problems which will be discussed in a separate communication. Of the 176 males 101 had no urological problem; in 34 there was blood at the external meatus or haematuria, so raising the suspicion of urethral or vesical injury. In 16 cases there was retention of urine, and in a further 25 massive associated injuries required intensive efforts at resuscitation.

Of the 101 cases in which there was no urological problem, 2 developed impotence; in neither of these men had a catheter been passed.

In 34 men haematuria or the presence of blood at the meatus raised the suspicion of associated urethral injury (Table 1). In 15 of these a soft narrow rubber catheter was passed. In one man (who was subsequently found to have positive

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Table 1 Fractured Pelvis: 34 Males with Haematuria or Blood at the Meatus

Catheter passed easily			
Previous GC stricture	1		15
Follow-up bouginage ×3	1		
Stricture 6 years later	1		
No problems	12		
Catheter failed to pass easily			
Explored and repaired			
No stricture	4	8	10
Annual bougie	2		
Urethroplasty	2		
Unfit for operation, suprapubic only (both strictured)		2	
Catheter not attempted			
Died in resuscitation	1		5
Microscopic haematuria	2		
Solitary renal stone	1		
Torn prepuce	1		
Laparotomy for associated rupture of bladder			
Died of head injury	1		4
Stricture, annual bougie	2		
No stricture	1		
Total			34

serological tests for syphilis) an old and presumably gonococcal stricture was noted as the catheter was introduced; in another a bougie was passed at decreasing intervals after he left hospital for the purposes of diagnosis rather than treatment, and a third patient returned 6 years later with a urethral stricture, possibly caused by the catheter.

In 10 patients the gentle attempt to pass a soft rubber catheter failed: in 8 of them the retropubic space was explored and an attempt made to mobilise the prostate and bring the torn ends of the urethra together over a narrow splinting catheter. Of these cases 4 recovered with no detectable stricture 5 years later; 2 still attend for annual dilatation (though it is questionable whether by now this is still necessary); 2 developed a stricture which needed urethroplasty. In 2 of the patients in whom the gentle passage of a narrow soft catheter failed, the general condition of the patient forbade exploration of the pelvis: both had a suprapubic cystostomy tube inserted, and both developed a stricture.

A further 5 patients had blood at the meatus or haematuria, but a catheter was not passed: in one it was because massive internal haemorrhage from associated injuries led to his death in the resuscitation room: in 2 the haematuria was disregarded because it was found only on microscopy and the patients were able to void without difficulty; in one patient the emergency IVU disclosed a calculus in a solitary kidney which was dealt with later on. In one patient the blood was obviously coming from a lacerated prepuce.

Laparotomy was indicated in 11 of the 176 men with fractured pelvis. In 4 patients with haematuria, a lacerated bladder was found in association with an injury to the membranous urethra: one of these died of his head injury, 2 attend for annual dilatation, and in one no stricture can be detected 4 years later.

In a further 41 patients a catheter was required for other reasons: in 16 it was because they developed retention of urine on being confined to bed with the fractured pelvis: none developed a subsequent stricture. In 25 a catheter was passed in the intensive care unit in order to monitor urine output as part of the treatment of the depleted blood volume: of these 2 were dialysed for anuria secondary to shock, 9 died of associated multiple injuries, but none of the survivors developed a stricture.

Urethral Strictures

This series consisted of 470 patients treated for urethral stricture from 1964 to 1978 at the London Hospital and by one firm at St Peter's Hospital.

Inevitably this series must be unrepresentative for 302 of the 470 cases underwent urethroplasty, often having been specially referred for that procedure. Of the entire series, 224 had a history of trauma (Table 2), but for the purpose of the present enquiry we have disregarded the 131 cases in whom the trauma was post-surgical, the 27 fall-astride perineal injuries not associated with a fractured pelvis, and the 4 men with urethral injuries caused by a variety of bizarre accidents to the penis. This leaves 62 males with urethral strictures caused by the fractured pelvis, to whom are added 5 patients whose urethral injury healed without a detectable stricture. We have attempted

Table 2 Urethral Strictures: all Cases with Traumatic Aetiology

Iatrogenic	*Dilatation* *70*	*Urethroplasty* *61*	*Total* *131*
Accidental			
Perineal, fall astride	6	21	27
Fractured pelvis	10	52	62
Penile injury	0	4	4
Total	86	138	224

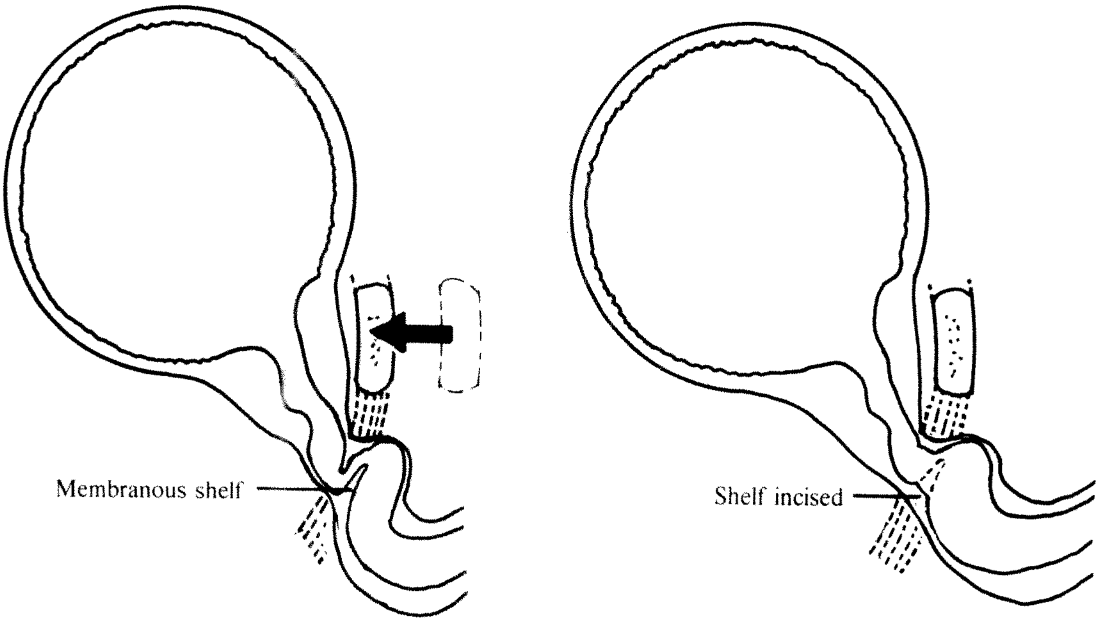

Fig. 1 An "easy" post-traumatic stricture is formed when the prostatic urethra comes to lie behind the membranous urethra, separated from it by a thin "shelf" which may be cut perurethrally, so avoiding the need for urethroplasty.

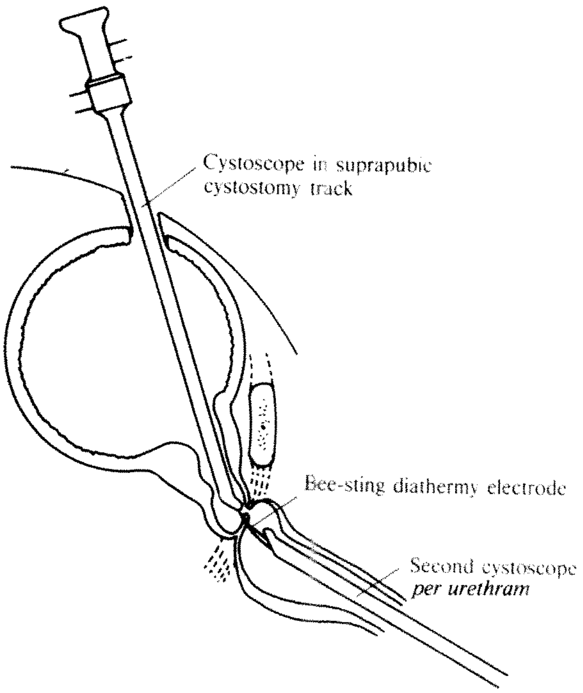
Cystoscope in suprapubic cystostomy track
Bee-sting diathermy electrode
Second cystoscope *per urethram*

Fig. 2 If the "shelf" is completely closed off, the light of a cystoscope introduced through the suprapubic cystostomy may reveal it to the second cystoscope passed *per urethram*, and the shelf may still be cut with the cold urethrotome or the bee-sting electrode.

to see how the initial management of these 67 patients affected the end-result, with particular concern as to the possible evil effects of initial diagnostic catheterisation and early surgical repair.

From the viewpoint of the patient post-traumatic strictures fall, we believe, into 2 groups—"good" and "bad". In the "good" group are those who have no stricture at all, or one that requires them only to attend at very infrequent intervals for the painless passage of a bougie. To these should be added those in whom the approximated ends of the urethra, though not completely aligned, are nevertheless separated (Fig. 1) by such a thin shelf or membrane that it can be successfully divided by an endoscopic knife or electrode (Fig. 2). In the past, before we recognised this as a regular entity, a number of 1- and 2-stage urethroplasties were performed whereas today they would be found unnecessary. If the shelf separating the 2 ends of the urethra is too thick to be cut with safety endoscopically, the shortness of the stricture still permits an easy one-stage urethroplasty using a dartos-pedicled pouch in the technique described by Gardiner *et al.* (1978). In many of these patients the antero-posterior radiograph shows little apparent bony deformity, but the lateral view (Fig. 3) shows that the symphysis has been displaced backwards, giving a characteristic S-shaped malalignment of the prostatic and membranous urethrae.

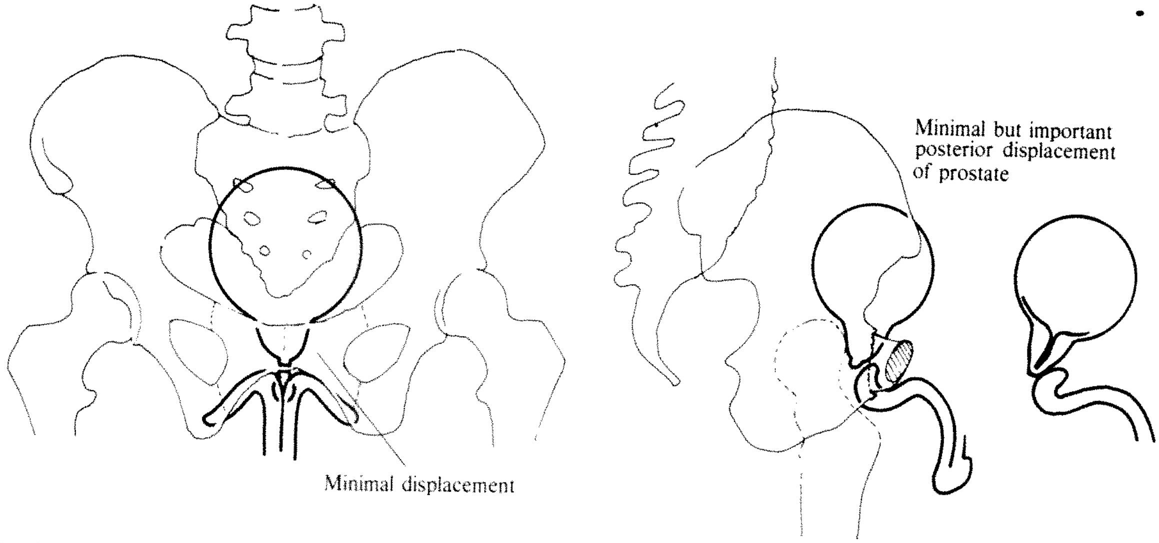

Fig. 3 (a) The anteroposterior X-ray of the fractured pelvis may show little apparent displacement but this may fail to reveal an important posterior displacement, (b) which results in a typical "easy" post-traumatic stricture.

In the "bad" strictures which follow fractured pelvis, there is nearly always gross displacement of the pelvic fragments (Fig. 4). If the ends of the urethra have not been mobilised and brought into proximity, they heal with a gap, filled with dense and difficult scar tissue. To cross this gap is a problem which taxes surgical ingenuity at the time of urethroplasty. In some cases a very high 2-stage scrotal flap urethroplasty has been used with success: in others a tubed-flap modification allows the scrotal skin to be brought up to the prostatic urethra: more recently the transpubic operation of Waterhouse *et al.* (1974) has been preferred by us as the procedure of choice for these difficult strictures.

When we looked at the method by which our patients with post-traumatic strictures had been treated in the first instance (Table 3), we were unable to get complete details in 20 of the 67 cases, and in a further 3 patients so many previous attempts at repair had been made elsewhere that it was unclear whether the stricture we were faced with was caused by the injury or the previous surgical intervention.

It is therefore not possible to state with conviction that one or other method of management is superior: where we have complete details, and there was a "good" stricture or none at all, an early attempt at surgical repair had been performed in 22 of 25 cases (88%). Where the result was "bad" a suprapubic cystostomy alone had been done in 7 of 19 cases (37%). However, when only a suprapubic cystostomy had been done it was usually because the patients had very severe multiple injuries, and similarly when the stricture called for a very difficult urethroplasty it was nearly always because there was a long gap and severe persisting bony deformity.

The same difficulty in obtaining accurate information beset our enquiry into potency (Table 4). In 24 patients the men were too old or could not be properly questioned; 5 were too young. Data were available in only 36—but of these 23 (64%) claimed to be potent. All of those who were impotent had had severe urethral injuries and crush injuries of the pelvis, usually with residual bony displacement.

Table 3 Initial Management of Ruptured Urethra

End-result	*Early surgical repair*	*Suprapubic cystostomy alone*	*Details not available*	*Total*
Good				
No stricture	5			5
Dilatation	5			5
Shelf cut	5			5
Pedicled island patch	2	2	5	9
Easy scrotal flap	5	1	7	13
Bad				
Difficult scrotal flap	2	6	2	10
Tubed scrotal flap	3	2	7	12
Waterhouse		6	2	8
Total	27	17	23	67

Table 4 Fractured Pelvis, Urethral Injury and Potency

	Potent	*Impotent*	*Under 12*	*No data*
No urological problem	99	2	—	—
Urethral injury	23	13	5	24

Discussion

Advances in the technique of urethroplasty have defined a distinct group of patients with post-traumatic membranous urethral stricture in whom the 2 ends of the urethra come to lie separated by a relatively narrow shelf or membrane. If this can be identified it may be cut endoscopically and the patient spared the need for any form of urethroplasty. In other cases, if the ends of the divided urethra can be brought near to each other, even if the shelf of tissue separating them is not so thin that it can be safely cut perurethrally, it poses an easy problem for urethroplasty at which a one-stage pedicled patch can be used or, if a 2-stage operation is to be done, the first stage is relatively easy.

Study of this material suggests that the major factor leading to a "bad" and difficult urethral stricture is uncorrected displacement of the pelvic bones, and that the advantage of an early surgical repair is that the prostate can be mobilised and brought into apposition with the membranous urethra from which it has been avulsed. In those who are most fortunate, early surgical repair may be followed either by no stricture at all, or by a stricture which is easily and safely dealt with without the need for a urethroplasty at any stage. Our data regarding impotence permit no rigid conclusions to be drawn, but it appears to be a complication of a severe fracture and related to the soft tissue injuries rather than to any particular technique used in managing the disrupted urethra.

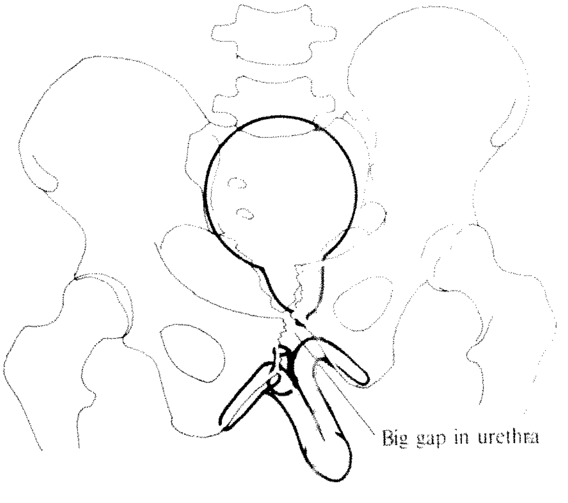

Fig. 4 "Difficult" strictures occur when there is gross bony displacement and the prostate has not been mobilised to bring the torn ends of the urethra into apposition.

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Urethral Tumours

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Summary—A series of 33 patients with urethral tumours has been studied to assess the risk of dissemination by endoscopic diathermy. This risk is less than that of cystourethrectomy. Urethral tumours should be treated like the vesical tumours they follow and so closely resemble: by endoscopic treatment while they remain small, sparse and superficial; by cystourethrectomy as soon as they become larger and more extensive.

Recurrence of tumour in the urethral stump following cystectomy should always be treated by urethrectomy.

Attention has been drawn to the risk of disseminating urethral tumours by diathermy (Hendry *et al.*, 1974) but the magnitude of the risk has yet to be assessed. If the risk is great then all urethral tumours should be treated by cystourethrectomy. If less than that of cystourethrectomy then superficial tumours of the urethra should be managed endoscopically in the same way as superficial tumours of the bladder.

This retrospective survey was performed to assess the magnitude of this risk.

Patients and Methods

Over the last 10 years 33 male patients undergoing follow-up for multiple superficial tumours of the bladder have developed urethral tumours. During this period there were approximately 660 male patients with new vesical tumours, so that the incidence of urethral tumours was 5%.

Thirty-two patients had papillary carcinoma of the bladder; 1 patient had a single, solid, superficial carcinoma of the trigone.

Twenty-six patients had carcinoma at the bladder neck; when small in extent an average of 5 years elapsed before urethral tumours developed, in contrast to an average of only 1 year when the extent was large (Table 1). There was no correlation between urethral involvement and the histological grade of the tumour.

In 6 patients the bladder had been recurrence-free before the urethral tumour developed. This period varied from 3 to 54 months; the mean was 20 months.

Urethral tumours occurred with decreasing frequency from the bladder neck to the external urethral meatus; in 48% of patients tumour was present in the prostatic urethra alone, in 6% in the anterior urethra alone, and in 46% tumours were scattered throughout the whole length of the urethra. When biopsy was performed it showed that the histological grade of the urethral tumour was similar to that of the vesical tumour.

In 8 patients ureteric tumours developed; their histological grade was similar to those of the lower urinary tract. In 3 patients the ureteric tumours were multiple and in 1 bilateral.

A cutting diathermy current, which produces more localised destruction compared to the coagulation current, was used for endoscopic treatment. Small anterior urethral tumours were usually destroyed using a fine electrode passed through an operating cystoscope. Only 4 tumours were biopsied. Similar treatment was given to small tumours in the prostatic urethra, but when biopsy was necessary or the tumours were more extensive, then transurethral resection was performed.

Table 1 Urethral Tumours Following Bladder Neck Involvement

Extent of involvement	*Patients*	*Average time interval between bladder neck and urethral tumours*
Small	10	5 Years (Range 1-10)
Large	16	1 Year (Range 0-6)

Read at the 34th Annual Meeting of the British Association of Urological Surgeons in Brighton, June 1978.

Table 2 Results of Endoscopic Treatment of Urethral Tumours

Treatment	*Patients*	*Outcome*	*Survival*	*Average follow-up*
Single	5	"Cured"	Alive	4 Years
	2	Cystectomy	Dead	-

Results

The results are considered in 2 parts, firstly after single endoscopic treatment, and secondly after repeated treatments.

Single treatment (Table 2)

Five patients with solitary or multiple tumours in the prostatic urethra have been considered "cured" by 1 endoscopic treatment. The average follow-up was 4 years.

Two patients had extensive tumour at the bladder neck growing down into the prostatic urethra: both patients had a single, small anterior urethral tumour diathermied endoscopically immediately prior to cystectomy. In 1 patient histological examination of the cystectomy specimen revealed tumour throughout the whole length of the prostatic urethra. The other patient developed invasive tumour in a different part of the urethra to the area diathermied. Both patients died of local and metastatic disease.

Repeated treatments (Table 3)

Twenty-six patients required repeated endoscopic treatments ranging from 2 to 21 with an average of 6 per patient. Sixteen of these patients appear to have been treated successfully by endoscopic means alone. The mean period of follow-up is 4 years; in 10 patients the urethra remains recurrence-free.

In 7 patients cystourethrectomy was required, usually because of poor endoscopic control of urethral tumours, but in 1 patient because of an invasive vesical carcinoma. All bladders contained carcinoma at the time of cystourethrectomy. The average period of follow-up from the start of urethral endoscopic treatment has been 5 years. In the patients treated by repeated endoscopic diathermy alone and those who later required cystourethrectomy, there was no evidence during the period of follow-up that the urethral tumour had been disseminated by diathermy.

Two patients, aged 75 and 80 years, were considered unfit for cystourethrectomy; 1 died from carcinomatosis, the other is alive following radiotherapy for an invasive carcinoma of the prostatic urethra.

In only 1 case out of 33 can it be considered that the urethral tumours were managed endoscopically for too long, resulting in deep invasion of the prostate and distant metastases.

Table 3 Results of Endoscopic Treatment of Urethral Tumours

Treatment	*Patients*	*Outcome*	*Survival*	*Average follow-up*
Repeated	16	Successful	Alive	4 Years
	7	Cystourethrectomy	Alive	5 Years
	2	Unfit	1 Dead	-
	1	Metastases	Dead	-

Discussion

Urethral tumours are found most commonly during follow-up of cases of carcinoma of the bladder. As primary tumours they are rare. The greater the extent of the tumour at the bladder neck, the more rapid is the urethral involvement. Biopsy of anterior urethral tumours in this series was performed in only 4 cases; it was usually thought unnecessary because the tumours appeared small, sparse and superficial and resembled the previous tumours of the bladder which had been easily controlled endoscopically. When it was thought necessary, biopsy of anterior urethral tumours was performed with Storz flexible forceps passed through the operating cystoscope. Deep biopsy is difficult and can lead to bleeding and stricture formation. The information biopsy provides is, therefore, on histological grade rather than on the stage of the tumour. Consequently it is the increase in size and number of urethral tumours, possibly associated with a worsening of histological grade, which raises the question of cystourethrectomy.

Hendry *et al.* (1974) quoted 4 cases to demonstrate the danger of disseminating urethral tumours by endoscopic diathermy. In 3 of these cases urethral diathermy was performed for tumours developing in the urethral stump after cystectomy. The inference of their article was that tumours of the anterior urethra should be treated by cystourethrectomy, not diathermy. Clearly all cases of recurrence in the urethral stump after cystectomy should be treated by urethrectomy.

In our patients and the cases reported by Hendry *et al.* (1974) there was only 1 case in each series of dissemination following diathermy when the bladder and urethra were intact. The incidence of such an event in this series is 3.5%. This compares favourably with the 5 to 10% operative mortality for cystourethrectomy and provides justification for the more conservative approach.

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Endoscopic Examination in Children

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Summary—Cystourethroscopy is an uncomfortable and often painful investigation for children. It is distressing to the parents, and even when it is done on a day case basis it can cause considerable disruption to the family. It should therefore only be considered when it is felt that the examination will contribute to the management of the urinary problem in the child, and then only after routine assessment including physical examination, urine culture, renal function studies, excretion urography and, where indicated, micturating cystogram.

In a study of 242 children who had cystourethroscopy, it was found to be of only limited value in children with enuresis, incontinence, haematuria, recurrent urinary infection and painful micturition. In some children it provided an opportunity for either indirect (from instrumentation) or formal urethral dilatation and this seemed to be associated with post-operative symptom relief in some children.

Endoscopy appeared to be of most value in the management of vesicoureteric reflux, upper tract duplication and specific urethral abnormalities. In these situations the examination provided essential information which was helpful with further management of the children.

Cystourethroscopy is an established and essential investigation of the urinary tract in the adult. Its role in the management of urological problems in childhood would seem less certain. In children, urethral instrumentation may present difficulties; furthermore, interpretation of the findings often requires considerable endoscopic experience.

A series of children undergoing endoscopic examination at the Bristol Children's Hospital has been reviewed to assess the role of this investigation in the management of their urinary problems.

Patients and Methods

Two hundred and forty-two children who have been investigated by cystourethroscopy have been reviewed. One hundred and forty-three were female and 99 male; the age incidence is shown in Figure 1. The examination was carried out in the investigation of many urological problems and the most common conditions have been analysed separately (Table 1).

The children were all assessed in the Out-patients Department and were then put on a waiting list for endoscopy. The endoscopy was carried out under general anaesthesia on a day case basis.

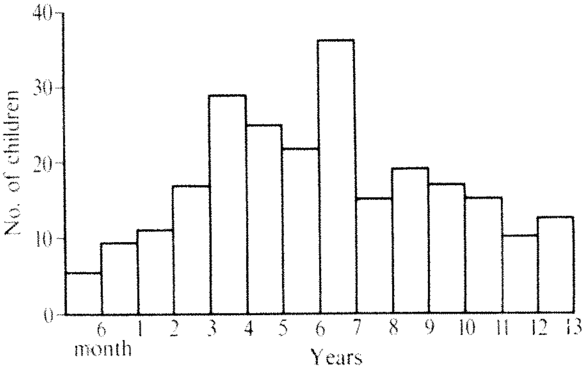

Fig. Endscopy in Children: Age Incidence

Table 1 Indications for Endoscopic Examination

Recurrent urinary tract infections	36
Vesicoureteric reflux	83
Painless haematuria	23
Enuresis	29
Incontinence	33
Painful micturition	14
Frequency (diurnal and nocturnal)	6
Urethral valves	4
Upper tract duplication	8
Trauma	2
Hypospadias	2
Ureterostomy	2
Total	242

Read at the 34th Annual Meeting of the British Association of Urological Surgeons in Brighton, June 1978.

Results

Recurrent Urinary Tract Infection

The results of investigation by culture of a mid-stream specimen of urine, excretion urography and micturating cystourethrography are shown in Table 2. The urine was reported as sterile in 7 children but they were all on antibiotics. Excretion urography was normal in 30 (83%). The findings on endoscopy are shown in Table 3. Urethral dilatation was performed in association with endoscopy in 11 children. Table 4 shows the change in symptoms at post-operative assessment 4 weeks following endoscopy.

Table 2 Endoscopy in Children with Recurrent Urinary Tract Infections

Investigations	*Patients*
MSU	
Sterile	7
Infected	21
Not stated	8
Excretion urography	
Normal	30
Upper tract dilatation	4
Reflux nephropathy	4
Bladder stone	1
MCUG	
No reflux	15
Grade I	0
Grade II	1
Grade III	4
Not performed	16
Total	36

Table 3 Recurrent Urinary Tract Infections—Endoscopic Findings

Normal	19
Inflamed trigone	7
Trabeculation	8
Patulous ureteric orifice	8
Tight urethra	2
Tight bladder neck	2
Bladder stone	1
Increased residual urine (>150 ml)	6

Vesicoureteric Reflux

Eighty-three children with diagnosed vesicoureteric reflux were investigated by endoscopy. These children had been treated conservatively and endoscopy was performed as an aid to further management. Investigations prior to endoscopy (Table 5) revealed that only 8 children had sterile urine. Thirty-one normal kidneys were seen on excretion urography. Micturating cystourethrography had demonstrated Grade III reflux in 63 children in this group.

Table 4 Recurrent Urinary Tract Infections—Symptoms following Endoscopy

Symptom-free	3 (1)
Improved	10 (6)
No change	16 (3)
Worse	1 (0)
No follow-up	6 (1)
Total	36

( ) = endoscopy and urethral dilatation

Table 5 Vesicoureteric Reflux—Investigations Prior to Endoscopy

MSU	
Sterile	8
Infected	67
Not stated	8
Excretion Urography	
Normal	31
Renal scarring	25
Upper tract dilatation	33
Thick walled bladder	2
Increased residual urine	4
Stone formation	4
Urethral valve	2
MCUG	
Grade I	3
Grade II	17
Grade III	63

Endoscopy revealed a normal bladder in only 13 children and abnormal ureteric orifices in 62 children (7 with duplex ureteric orifices and 55 with patulous ureteric orifices). In 66 children (80%) with vesicoureteric reflux, reimplantation was carried out soon after endoscopy, whilst in only 17 children was a conservative regime continued (Dunn *et al.*, 1978).

Painless Haematuria

Painless haematuria was investigated in 23 patients, in none of whom was the urine infected. No significant abnormality was detected on excretion urography. The endoscopic findings were normal in 21 children. One child had a small angioma in the bulbous urethra but this was not removed and there was no further bleeding. One child was noted to have prominent veins over the bladder neck.

Five children had persisting haematuria following endoscopy. Two were subsequently diagnosed as post-streptococcal glomerulonephritis. One patient stopped bleeding after a circumcision and another after an upper moiety nephroureterectomy. No cause for the persisting haematuria was found in the remaining case.

Enuresis

Twenty-three of the 29 patients with enuresis had life-long or primary enuresis, and only 1 child had a urinary infection. Excretion urography was normal in 25 cases. Two children had a thick walled bladder and 2 had residual urine. One patient had a non-functioning kidney. Endoscopy revealed trabeculation in 8 children whilst in 3 a tight bladder neck was described. One had a tight urethra (Table 6).

Table 6 Enuresis—Endoscopic Findings

Normal	19
Mild trabeculation	5
Moderate trabeculation	3
Tight bladder neck	3
Tight urethra	1
Patulous ureteric orifice	4

Enuresis resolved following endoscopy in 2 children (Table 7).

Table 7 Enuresis—Symptoms following Endoscopy

Symptom-free	2
Improved	4
No change	18
No follow-up	4

Incontinence

Thirty-three children with incontinence were investigated by endoscopy, 28 having diurnal and nocturnal incontinence, 4 diurnal incontinence and urgency, and 1 dribbling incontinence. Table 8 shows the findings of investigations prior to endoscopy, and the results of endoscopic examination are shown in Table 9. Seven children had an empirical dilatation performed at the time of endoscopy. Two patients became symptom-free and 10 were symptomatically improved following endoscopy (Table 10).

Table 8 Incontinence—Investigations Prior to Endoscopy

MSU	
Sterile	16
Infected (*E. Coli*)	7
Not stated	10
Excretion Urography	
Normal	28
Pelvic hydronephrosis	1
Bilateral hydronephrosis and hydroureter	1
Renal agenesis	2
Not stated	1
MCUG	
Reflux	7
No reflux	10
Not performed	16

Table 9 Incontinence—Endoscopic Findings

Normal	14
Trabeculation	11
Oedamatous mucosa	5
Tight urethra	1
"Trigonal hyperaemia"	1
Urethral diverticulum	1
Patulous ureteric orifice	2
"Raised" bladder neck	1
Bladder diverticulum	1
Tight external urethral meatus	1
Absent ureteric orifice	2
"Filthy perineum"(!)	2

Table 10 Incontinence—Symptoms following Endoscopy

Symptom-free	2 (2)
Improved	10 (2)
No change	17 (3)
Worse	1
No follow-up	3
Total	33

( ) = endoscopy and urethral dilatation

Painful Micturition

Fourteen children with painful micturition have been reviewed. In 2 the urine was infected. Excretion urography suggested a trabeculated bladder in 1 child and revealed renal agenesis in another. Physical examination demonstrated 2 children with phimosis, 1 with a meatal stenosis and 1 with acute on chronic retention of urine.

At endoscopy 3 children were found to have a tight external urethral meatus and 1 had marked trabeculation. The absence of a ureteric orifice in the child with renal agenesis was confirmed.

At follow-up the 4 children who had had meatotomy and/or circumcision were symptom-free. Only 1 child remained symptomatically unchanged although 7 failed to attend for follow-up.

Upper Tract Duplication

Eight children with upper tract duplication presenting mainly with urinary tract infection have been investigated. In each case endoscopy confirmed the state of the duplication and revealed the anatomical appearance and arrangement of the ureteric orifices in the bladder. This information made an important contribution to the subsequent surgical management.

Other Conditions

Investigations of the 6 children with frequency failed to reveal any abnormality on urine culture or excretion urography. Endoscopy revealed a trabeculated bladder in 1 child. One patient who improved following endoscopy had a simultaneous hydrostatic dilatation.

The 4 children with urethral valves presented with febrile illnesses and in 1 a febrile convulsion. Urethral valves were diagnosed on excretion urography and micturating cystourethrography. Endoscopy was used to localise the urethral valves prior to endoscopic destruction.

Two children had endoscopy to assess urethral trauma. Two children with hypospadias have had endoscopic examination. In one, endoscopy was carried out prior to urethroplasty and in the other child for spraying stream following hypospadias repair.

Two children who had had cutaneous ureterostomies for gross vesicoureteric reflux had endoscopic examinations carried out to assess the urethra, bladder neck and bladder, prior to vesicoureteric reimplantation.

Complications

There were only 2 complications to endoscopy in these 242 cases. One child developed retention after cystoscopy but this settled after a period of catheter drainage. One child had anaesthetic problems during extubation but suffered no ill effects.

Discussion

The role of cystourethroscopy in the investigation of children is not clearly defined. Problems may arise from the procedure in that the urethra of a child, in particular the male, may present difficulties in instrumentation and urethral damage may result. The interpretation of the small field of view, even with modern fibre optic equipment, requires considerable endoscopic experience.

It should not be forgotten that endoscopy in children may be a distressing investigation for both the child and its parents. Anaesthesia also is not without risk. In order, therefore, to justify such a procedure in children it is necessary to be sure that the investigation will contribute to the subsequent management of the case.

From this review it would seem that endoscopy is of limited value in children with recurrent urinary tract infections in whom excretion urography is normal and there is no evidence of vesicoureteric reflux. In some children with persistent symptoms, despite antibiotics, endoscopy itself, or in combination with formal urethral dilatation, may produce symptomatic improvement (Graham *et al*., 1967). The role of urethral dilatation in the management of these cases, however, remains contentious (Smith, 1969).

Endoscopy was an important aid in the management of vesicoureteric reflux. Those children with patulous and/or lateralised ureteric orifices are best identified by endoscopy. Endoscopy in children with such abnormalities of the ureteric orifices, in association with clinical and radiological studies, usually shows them to have a severe degree of reflux requiring surgical rather than conservative treatment. Endoscopy will also aid in the management of reflux associated with ureteric duplication. Finally, in the presence of unilateral reflux (as shown on micturating cystourethrography) endoscopy may indicate the need for bilateral reimplantation and hence reduce the incidence of post-operative contralateral reflux.

Unlike the adult, the usual cause of haematuria in children is glomerulonephritis (Harrison *et al*., 1966). This is a benign and usually self-correcting condition with a good prognosis (Wyatt *et al*., 1976). Tumours of the urinary tract in children are diagnosed effectively by physical examination and excretion urography (Wyatt *et al*., 1976). In this series endoscopy for haematuria contributed to the management of only one child (urethral angioma).

Whilst endoscopy revealed no significant abnormality in children with enuresis it is interesting to speculate as to why 2 children became symptom-free following endoscopy. Possibly the incidental urethral and bladder dilatation associated with the procedure may have contributed to the resolution of enuresis.

In the 33 children with incontinence, endoscopic examination contributed to management in only 2 cases; in one it helped to establish the diagnosis of vesicoureteric reflux requiring surgical correction, and in another a urethral diverticulum was discovered. It is worth noting that in this group the simplest investigation, MSU culture, revealed 7 children with urinary infection, a far more important finding than any at endoscopy. In the same way, those children with painful micturition were better investigated by routine physical examination than endoscopy. Whereas endoscopy revealed no obvious lesion the physical examination showed phimosis, meatal stenosis and in one child urinary retention.

However, there is no doubting the assistance given by endoscopy in the management of children with urinary problems associated with ureteric duplication. Though none of the children studied had an ectopic ureter, in the absence of duplication endoscopy is the investigation of choice in locating the ectopic orifice. It also provided essential information in the children with the less common problems of urethral abnormality such as urethral valves and stricture, either traumatic or post-operative.

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Indications for Testicular Biopsy or Exploration in Azoospermia

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Summary—Investigation of 311 azoospermic males has shown that the combination of estimation of testicular size and plasma FSH allows the spermatogenic function of the testes to be accurately assessed by non-invasive methods.

Patients with small testes and grossly elevated levels of plasma FSH have absent, or grossly impaired spermatogenesis, and do not require surgical exploration. They should be advised with regard to adoption or artificial insemination.

Patients with large testes (5 cm) or an FSH level which is not grossly elevated require operation and should undergo a surgical exploration and the possible correction of an obstructive lesion. A testicular biopsy is essential if no obstructive lesion is found as the histology of these patients may show a spermatogenic arrest.

Azoospermia is usually considered to be an indication for a testicular biopsy as part of the investigation of an infertile man. Histological examination of the testes gives a clear assessment of spermatogenesis and allows a rational choice for the future management of the couple by reconstructive surgery, hormonal therapy, artificial donor insemination or adoption.

In a previous paper we showed that the estimation of immunoreactive follicle stimulating hormone (FSH) by radioimmunoassay gave an excellent guide to spermatogenesis (Pryor *et al.*, 1976). In the present paper we have extended the hormone studies but have shown that even where there is normal spermatogenesis it is often still impossible to correct the obstruction.

Materials and Methods

Three hundred and eleven male partners of an infertile couple attended King's College or St Peter's Hospitals during the period 1975 to 1977 and were found to be azoospermic on 2 occasions. They attended for the investigation of infertility and have been studied by the following methods.

Testicular size was assessed by comparison of the testes with a graduated rosary of wooden ovoids—2, 3, 4 or 5 cm in length. Plasma FSH levels were estimated by radioimmunoassay using the reference preparation MRC 69/39 (32.8 units per ampoule) in 1975 to 1977. The normal range for this assay was 0.8 to 3.4 u/l and the results have been categorised as normal, elevated between normal and twice the upper limit of normal (6.8 u/l) and grossly elevated when the level was more than twice normal. Since May 1977 a new reference preparation has been used (69/104) but the same numerical limits have been used for this paper. The normal range of FSH with this assay has recently been established as 0.8 to 5.6 u/l.

Surgical exploration of the testes was undertaken in most patients during the period 1975 to 1976 but after that time only when the FSH levels were not grossly elevated. At operation the epididymis was inspected and its appearance noted. The appearances have been retrospectively graded as shown in Table 1. Patency of the vas deferens was confirmed by the injection of 45% hypaque or saline and reconstruction procedures were carried out as indicated. A small testicular biopsy, often bilateral, was taken and the specimen was placed in Bouin's solution. The histological sections were stained with haematoxylin and eosin and spermatogenesis was assessed by the Johnsen

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Table 1 Visual Assessment of the Epididymis

N	Normal
±	Occasional dilated tubule
+	Dilated tubules but "solid"
+ +	Dilated tubules full of fluid

The level of collapsed epididymis was noted.

technique (Johnsen, 1970). Spermatogenesis is absent when the mean Johnsen score is less than 2.0 and a useful degree of spermatogenesis is present when the mean Johnsen score is greater than 8.0. Chromosome studies were carried out on peripheral blood if Klinefelter's syndrome was suspected.

Results

Non-Invasive Assessment of Spermatogenesis

These findings confirm our previous results and are summarised in Tables 2 and 3.

It is important to consider the plasma FSH level in relationship to the size of the testes before coming to a conclusion with regard to the likely absence of spermatogenesis. In this respect it should be noted that when one testis is absent or small there may be some elevation of the FSH level even though spermatogenesis is proceeding actively in the normal testis.

If there is a discrepancy between the clinical findings and the result of the plasma FSH levels it is important that the plasma should be retested, as even when reliable preparations are used (for example, those supplied by the World Health Organisation) and with good quality control (intra-assay variation of 14.0% and an inter-assay variation over one year of 25.1%), errors may occur. The recent change in the range of normal immunoreactive plasma FSH levels has led to little change in the classification of the patients. When spermatogenesis is absent the plasma FSH levels are usually elevated far above twice the upper limit of the normal range. The mean for 35 patients with 2 cm length testes and absent spermatogenesis (demonstrated by biopsy in 11 patients and Klinefelter's syndrome in an additional 13 patients) was 38.4 u/l.

Table 2 Relationship between Testicular Size and Mean Johnsen Score in 364 Testes from Azoospermic Men

Testis size (cm)	*Number of testes*	*Mean Johnsen Score (No./%)*		
		<2.0	2.1-7.9	>8.0
2	11	11(100)		
3	57	34(60)	22(38)	1
4	108	39(36)	30(28)	39(36)
5	188	11(6)	33(18)	144(76)

Table 3 Relationship between Plasma FSH and Mean Johnsen Score in 214 Azoospermic Men

FSH (u/l)	*Number*	*Mean Johnsen Score (No./%)*		
		<2.0	2.1-7.9	>8.0
"Normal" 0-3.4	114	4(3.5)	26(23%)	84(73.5)
"Elevated" 3.4-6.8	26	6(23)	12(46)	8(31)
"Grossly elevated" >6.8	74	54(73)	16(22)	4(5%)

The Results of Testicular Exploration

The results are considered only in those patients in whom the FSH level was not grossly elevated or the testes were of normal size.

1. Appearance of the Epididymis One hundred and sixteen epididymes appeared normal and on these occasions the testicular biopsy showed absent spermatogenesis in 20 (17%), impaired spermatogenesis in 56 (48%) and active spermatogenesis in 40 (34.4%). Two hundred and fifty-eight epididymes contained dilated tubules and on such occasions the testicular biopsy showed spermatogenesis with the mean Johnsen score usually in excess of 8.0.

2. Spermatogenic Arrest The testicular histology of 9 patients showed a spermatogenic arrest which was usually at the level of step 5, *i.e.* at spermatocyte level. This group had good sized testes (4 or 5 cm), but the FSH levels were variable. In those patients with an FSH deficiency the level was always at the lowest level of the assay. It has been possible to treat one such patient with Pergonal to restore spermatogenesis and his wife has successfully been delivered of a normal child.

3. Vasa Aplasia Twenty-one patients had a bilateral absence of the vas deferens. This defect should be detected clinically and a testicular biopsy is clearly unnecessary. Nevertheless, 10 patients referred from other hospitals had already had a testicular biopsy and 9 of them were referred for an epididymovasostomy. The mean

Johnsen score of the testicular biopsies in this group was 8.6±0.7 (N=23).

4. *Reversal of Vasectomy* Forty-two patients were operated upon in an attempt to reverse a previous vasectomy and in each of these the epididymis was dilated and contained clear or opalescent fluid. The mean Johnsen score of the testicular biopsies was 8.6±0.5 (N=51) which is not significantly different from the score in other forms of obstruction. Thirty-three (88%) out of 37 men are known to have spermatozoa in the ejaculate following vasovasostomy and 8 of their wives have already conceived.

5. *Epididymovasostomy* Eighty-four patients were considered as candidates for an epididymovasostomy. This was not always possible because there were no sperms in the epididymis in 20 patients or because a proximal block in the vas deferens was demonstrated by vasography in a further 20 patients. In 21 patients the epididymes contained either a few dilated tubules or the tubules in the caput epididymis were filled with thick inspissated material which had to be excised. None of the epididymovasostomies in these patients was successful. There remains a group of 22 patients where the dilated tubules of the epididymis—usually caput—contained opalescent fluid and 4 of them are known to have spermatozoa in the ejaculate (maximum of 49 million). The mean Johnsen scores of the testicular biopsy in this favourable group of epididymovasostomy patients was 8.7±0.5 (N=32).

The appearances of the epididymis and the vasograms are often dissimilar on the 2 sides and on 3 occasions it has been necessary to do a crossed epididymovasostomy or vasovasostomy.

Discussion

The relationship betweeen plasma FSH levels and the stage of spermatogenesis was shown by Franchimont *et al.* (1972) and de Kretser *et al.* (1972). The clinical value of this finding was shown in our earlier study and is confirmed by the present larger series. Active spermatogenesis was found to be taking place in the testes of 5% of patients with grossly elevated FSH levels but by taking testicular size into account it is possible to eliminate such errors of assessment. Patients with absent spermatogenesis do not require testicular biopsy or exploration, and the combination

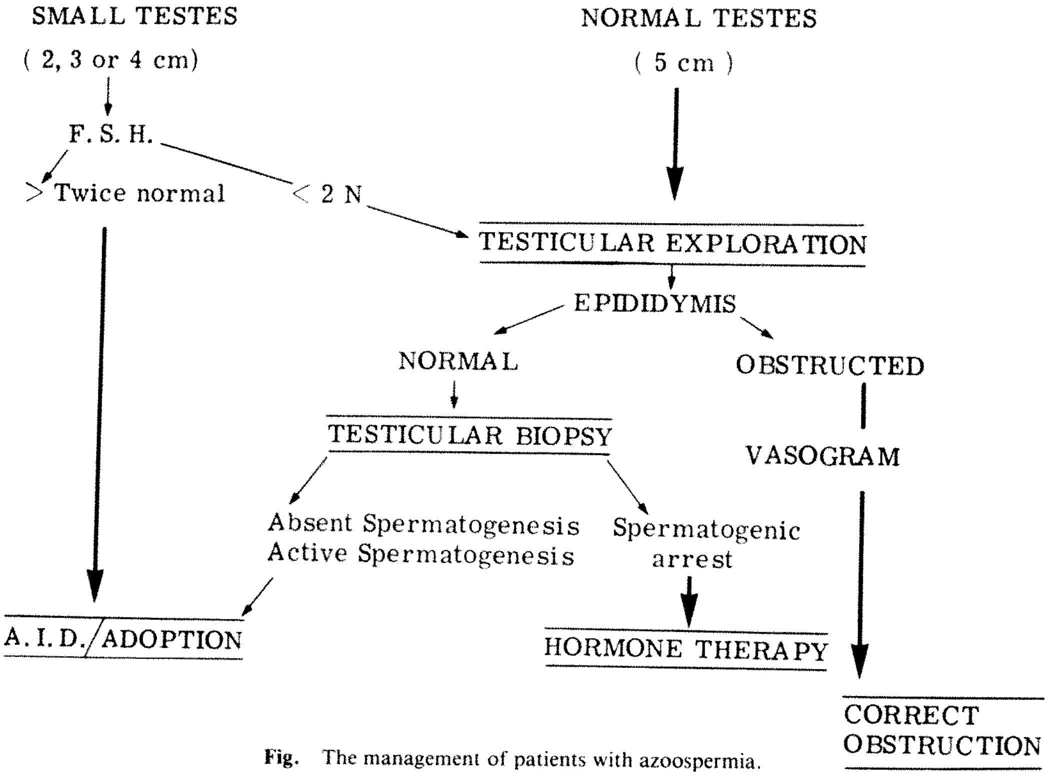

Fig. The management of patients with azoospermia.

of a gross elevation of FSH level and small testes (2, 3 or 4 cm) is sufficient evidence on which to advise the patient to consider the alternatives of adoption or artificial insemination. In those patients who require an operation the epididymis should be inspected, as even when active spermatogenesis is confirmed it is not possible to carry out an epididymovasostomy in 50% of patients. Surgical exploration should, therefore, be undertaken with the object of correcting the obstruction at the initial operation, as inspection of the epididymis gives a reliable guide to an obstructive lesion. If the epididymal tubules are not distended an epididymovasostomy should not be performed as it is in this group that the testicular histology sometimes shows a spermatogenic arrest and care must be taken not to produce an obstructive lesion.

In conclusion, the clinical role of testicular exploration in an azoospermic man is summarised in the figure. It can be seen that a biopsy is essential only in those patients with a gross elevation of FSH levels and in whom the epididymis looks normal on surgical exploration.

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The Management of Azoospermia

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Summary—Azoospermia in the presence of a normally functioning testis and a normal vasogram has been thought to be due to an obstruction in the epididymis between the body and the head. However, bypass operations have been singularly unsuccessful except when there was evidence of past inflammation causing fibrosis of the body and tail of the epididymis. Two substances, glycerylphosphorylcholine and carnitine, which are known to be secreted by the epididymis, were investigated. The results of this preliminary study suggest that they may play a part in the management of patients presenting with azoospermia.

Male infertility may result from many causes but amongst the 2 most important are failure in spermatogenesis, when the testes do not produce normal mature sperms, and obstruction to sperm transmission when normally produced sperms do not reach the ejaculate because of some lesion between the epididymis and the opening of the ejaculatory ducts.

In the management of male patients presenting with infertility a careful history, clinical examination and seminal analysis, carried out on at least 2 occasions, are mandatory. Also included in this initial assessment is a testicular biopsy on the result of which future treatment is largely dictated, as it differentiates between the "obstructive" and "non-obstructive" lesions. At the time of the biopsy the epididymis is examined as the head may be enlarged with many blue zones on the surface interspaced with yellow areas commonly accepted as dilated ducts. Whilst there are many causes of obstruction, such as gonorrhoea, non-specific epididymitis, tuberculous epididymitis, filariasis, smallpox, and following surgical procedures such as those for hernia repair and hydrocoeles, there are others which are called "idiopathic" as no obvious pathology can be found. It is this latter group which has been treated by epididymovasostomy with very poor results.

As epididymovasostomy had been such a failure in our hands it was felt that bypassing the body and tail of the epididymis might be a factor governing the poor results, as maturation of the sperms is said to occur during their passage through the body and tail. A series of epididymo-epididymostomies was therefore performed, excising an area of 1½ to 2 cm between the body and the head and then anastomosing the 2 parts in the hope that this procedure would overcome any obstruction and allow sperms to pass through the body and tail to the vas. The results of this surgical procedure were no better than those of epididymovasostomy. For more than 20 years it has been known that 2 substances, glycerylphosphylcholine (GPC) and carnitine, were present in high concentration in the seminal fluid. It was further reported that GPC was secreted largely in the head of the epididymis (Crabo *et al.*, 1967), and that carnitine was produced mainly in the body and tail (Frenkel *et al.*, 1974). This information suggested that the 2 substances might be used as a test to exclude obstruction. Table 1 shows what should be the findings theoretically if the obstructive theory was correct.

Table 1 Theoretical Findings Related to GPC and Carnitine in Azoospermic Patients if Obstructive Theory is Correct

Johnsen count <3: Normal GPC and carnitine
Johnsen count >8
  Obstruction at level of rete testis:
    Normal GPC and carnitine
  Obstruction between head and body of the epididymis:
    Low GPC
    Normal carnitine
  Obstruction in the tail of the epididymis:
    Low GPC
    Low carnitine

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Table 2 Mean ±SD GPC and Carnitine Results in Vasectomy Patients

	GPC mg/100 ml *36 patients*	*Carnitine μmol/l* *18 patients*
Pre-vasectomy	126.2±52.5	407.7±216.7
4 weeks post-vasectomy	31.6±16.7	128.0± 70.0
8 weeks post-vasectomy	37.1±25.7	73.3± 40.7
12 weeks post-vasectomy	40.1±20.08	78.8± 66.6
Total post-vasectomy	35.4±19.9	93.4± 48.6

The objective of this paper is twofold: firstly to explore the mechanism of obstruction in the epididymis and secondly to suggest a management of these patients which may prevent needless testicular biopsies and even epididymovasostomy.

Patients and Methods

The GPC was estimated by a modification of an enzymatic method (Michal and Lang, 1974) following acid hydrolysis (Brooks *et al.*, 1974). The carnitine was determined by a modification of an enzymatic method (Marquis *et al.*, 1964) following precipitation of protein and neutralisation of the supernatant fluid (Cederblad and Lindstedt, 1972). The modification of these methods is being published in detail elsewhere.

Control standards were established using vasectomy patients. The seminal fluid of 36 vasectomy patients was examined for GPC and carnitine immediately prior to vasectomy and 4, 8 and 12 weeks afterwards. The results were compared with those obtained with patients with bilateral absence of the vasa, oligozoospermia and azoospermia.

Results

The results before and after vasectomy are shown in Table 2, and demonstrate that once the vas was tied there was a marked and permanent reduction in GPC and carnitine in the seminal fluid. The number of patients in whom carnitine was estimated is less as there was not always enough seminal plasma to carry out both estimations. As confirmatory evidence the seminal fluid of 9 patients who had bilateral congenital absence of the vas, and body and tail of the epididymis, was examined. In 3 of these there was not enough seminal plasma to estimate GPC, suggesting a coincidental absence of the seminal vesicles, but in 6 the GPC was estimated and the results are shown in Table 3. Oligozoospermic patients (patients with a count <20 mil/ml) were then examined and Table 4 shows the results compared with the pre-vasectomy controls. Although the quantities were lower they were not as low as those obtained after the vas had been tied. The third group consisted of azoospermic patients and the results are shown in Table 5. Again the quantities are lower than the pre-vasectomy amounts and they are very similar to the amounts in the seminal plasma of oligozoospermic patients. In both the oligozoospermic and azoospermic patients the results were not affected by testicular function as measured by the Johnsen count. Table 6 shows the consolidated results of all the investigations.

Table 3 Mean ±SD Results in Azoospermic Patients with Congenital Absence of the Vas Compared with Pre-vasectomy Controls

Pre-vasectomy controls	126.2±52.5
Congenital absence of the vas (7 patients)	30.4±19.9

Table 4 Mean±SD GPC and Carnitine Results in Oligozoospermic Patients Compared with Pre-vasectomy Controls

	GPC mg/100 ml	*Carnitine μmol/l*
Pre-vasectomy control	126.2±52.5	407.7±216.7
Oligozoospermic patients		
Johnsen count 2-8 (12 patients)	107.5±48.97	275.6±106.1 (8 patients)
Johnsen count 8-10 (17 patients)	83.8±42.60	182.1± 54.7 (8 patients)

Discussion

GPC and Carnitine

GPC and carnitine are found in high concentration in the seminal fluid (Casillas, 1972; Frenkel *et al.*, 1974), but the function of each is still not

Table 5 Mean ±SD GPC and Carnitine Results in Azoospermic Patients Compared with Pre-vasectomy Controls

	GPC mg/100 ml	*Carnitine μmol/l*
Pre-vasectomy control	126.2±52.5	407.7±216.7
Azoospermic patients		
Johnsen count 2-8 (21 patients)	85.1±52.6	284.9±122.39 (21 patients)
Johnsen count 8-10 (18 patients)	80.64±44.43	280.2±116 (6 patients)

Table 6 Consolidated Results (mean ±SD)

	GPC mg/100 ml	*Carnitine μmol/l*
Pre-vasectomy	126.2±52.5	407.7±216.7
Total post-vasectomy	35.5±19.9	93.4± 70.7
Congenital absence of the vas	30.4±19.9	—
Oligozoospermic patients	94.45±38.6	228.9± 80.4
Azoospermic patients	82.8±48.5	282.6±119.20

fully understood. It is believed that GPC is largely secreted (75%) in the head of the epididymis (Riar *et al.*, 1973), and that the epididymis supplies 70% of the GPC found in the seminal plasma. Carnitine, however, is secreted mainly by the body and tail of the epididymis (Frenkel *et al.*, 1974) which supplies about 60% of the carnitine found in the seminal fluid.

If this work is accepted, it is reasonable to assume that if there is an obstruction between the head and the body of the epididymis the GPC in the seminal plasma should be low and the carnitine unaffected. However, as the results of this study have shown very little difference between the amount of GPC and carnitine in azoospermic and oligozoospermic patients, either the theory of obstruction is incorrect or GPC and carnitine are secreted in equal amounts in the body and tail of the epididymis.

The investigations so far indicate that the second suggestion may be correct as the assumptions of Riar *et al.* (1973) were made on rather thin evidence, mostly derived from mammals other than man; the human figures were based on the examination of only one epididymis. Furthermore, the reduction in the amount of the 2 substances in azoospermic patients when compared with pre-vasectomy patients suggests some change in function rather than obstruction, especially as the amount of GPC and carnitine is comparable irrespective of whether the epididymis appears macroscopically normal or has an enlarged head with many blue and yellow areas.

These are preliminary results and further investigations are proceeding, but at this stage of the study it is suggested that only if the GPC and carnitine are low and the FSH is normal should exploration of the testis and vasogram be carried out, as these findings could indicate a normal functioning testis with an obstruction proximal to the tail of the epididymis.

Acknowledgement

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Obstructive Azoospermia: Respiratory Function Tests, Electron Microscopy and the Results of Surgery

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Summary—Forty-five patients have been treated surgically for obstructive azoospermia. Fifteen underwent reversal of vasectomy and 40% of the wives became pregnant. Thirty had epididymovasostomy, and in only 2 (6.5%) did the sperm count become normal, although a few poorly motile sperms appeared in the ejaculate in a further 4 patients.

Congenital abnormalities of the vasa in 7 cases and post-inflammatory blocks in 4 cases were examples of obstructive azoospermia due to well defined causes. However, in half of the patients (15 cases) the cause was obscure although it was associated with sinusitis, bronchitis or bronchiectasis (Young's syndrome).

The results of pulmonary function tests in 30 cases, and electron microscopic studies of cilia from epididymes (10 cases) and bronchial mucosa (2 cases) indicated that the basic abnormality might be malfunction of the microtubules which appeared to be ultrastructurally normal in most cases. One case appeared to be associated with dietary deficiency, and correction of diet coincided with a successful result of surgery.

Obstructive azoospermia may be primary or secondary. The distinction is important because surgical correction may succeed with acquired blocks—for example in reversal of vasectomy, or in by-passing post-gonococcal epididymal obstruction. The success rate with primary obstructive azoospermia, on the other hand, is so poor that Hanley and Hodges (1968) were led to suspect a congenital failure of sperm propulsion through the epididymis rather than a simple blockage. A clue to the cause of the failure of sperm transport was provided by Young (1970) who observed significant defects in the lungs, including bronchitis and bronchiectasis, in 54% of 52 men with obstructive azoospermia.

There are at least 2 well-defined links between chest disease and sterility. Firstly, patients with cystic fibrosis may have congenital absence of the vasa with malformation of the epididymis (Holsclaw, 1969). Secondly, patients with Kartagener's syndrome (*situs inversus*, chronic sinusitis and bronchiectasis) may have immotile cilia due to an ultrastructural abnormality which also affects the sperm tails (Eliasson *et al.*, 1977); in these patients the sperm count is normal, but all the sperms in the ejaculate are non-motile. The association between primary obstructive azoospermia, when the vasa are present and sperm transport fails at the junction of the upper and middle thirds of the epididymis, and chronic chest disease, is clearly different from the 2 syndromes described above, but it may be due to similar pathological mechanisms. In order to study this association, and in the hope of improving the results of treatment, we have investigated in detail 30 men who had epididymovasostomy and compared the results of surgery with those obtained in a further 15 men who had vasovasostomy for reversal of vasectomy.

Patients and Methods

Vasovasostomy

Fifteen men had reversal of vasectomy by side-to-side anastomosis using 6/0 Prolene and no splint (Fig. 1).

Epididymovasostomy Groups

Thirty men with azoospermia, large testes and normal FSH levels were admitted and the purpose

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Read at the 34th Annual Meeting of the British Association of Urological Surgeons in Brighton, June 1978.

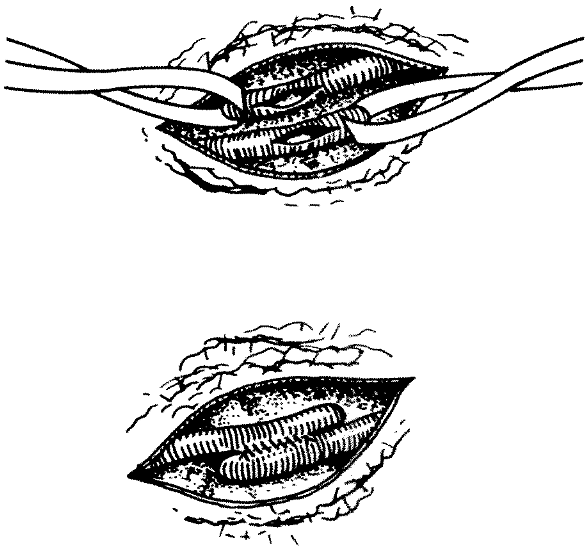

Fig. 1 Vasovasostomy by side-to-side anastomosis using 6/0 Prolene and no splint.

of the investigations was explained. Blood was taken for full blood count, prothrombin time, serum iron, B 12 and folate, urea and electrolytes, fasting blood sugar, liver function tests, gamma-glutamyl transpeptidase, serum 5-nucleotidase, alpha-1-antitrypsin titre, serum carotenoids and bacterial agglutinins. Three separate specimens of sputum were examined, and skin tests for atopy were done using 28 antigens. Pulmonary function tests and exercise tests were done including spirometry, lung volumes and gas transfer. Two sweat tests were done, and pancreatic juice was examined for tryptic activity. The chest and nasal sinuses were X-rayed, together with wrist and hand for bone age. In 5 selected patients with chest symptoms mucociliary function was investigated by measurement of clearance of Technetium 99^{m} – labelled polystyrene particles (5 micron diameter) (Thomson and Short, 1969).

Under general anaesthesia the scrotum was opened by a midline incision. The testes were delivered and the vaginal spaces were opened. The epididymes were examined and photographed. The vas was picked up and incised across the tunica vaginalis, and bilateral vasography was done using up to 10 ml of 25% Hypaque. The epididymis was then incised over the lowest part containing dilated tubules, and expressed fluid and a small epididymal biopsy were sent for histology and electron microscopy before completing the epididymovasostomy using 6/0 Prolene and no splint (Figs. 2a and b). Testicular biopsy was taken only in patients without sperms in the epididymis. Two patients with severe bronchiectasis underwent bronchoscopy and bronchial mucosal biopsy.

Seminal specimens were examined at 3, 6 and up to 12 months after operation, and all patients were contacted for news of possible pregnancy in the spouse.

Results

Vasovasostomy

The results of reversal of vasectomy are shown in Table 1. Six of 15 wives became pregnant, a success rate of 40%.

Table 1 Results of vasovasostomy

Number of patients	*Post-operative Sperm Count*				*Pregnancy in spouse*
	Unknown	*0*	*<20*	*>20 m/ml*	
15	3	1	4	7	6 (40%)

Epididymovasostomy Groups

The findings at scrotal exploration are shown in Table 2. Three patients (Group I) had no sperms in the epididymes: the findings on testicular biopsy and possible contributory factors are noted in the Table.

The findings on vasography (Table 3) have been used to subdivide the patients further according to the probable cause of obstruction. Various malformations of the vasa were found in 7 cases (Group II). In 4 cases there was a history of previous inflammatory disease (Group III) and in 3 of these patients additional blocks were found in the vas on one side, and corrected by additional vasovasostomy. In 16 patients the vasograms were normal (Groups IV and V).

The sperm counts after epididymovasostomy related to the probable causes of obstruction are shown in Table 4. The sperm count became normal in 2 patients (6.5%):

Case 1

Twenty-nine-year-old man said to have fathered 2 children before marriage. Right epididymal block with 2 blocks in right vas; left epididymal block. Histological examination of excised segment of vas showed post-inflammatory stricture. Sperm count 1 year after

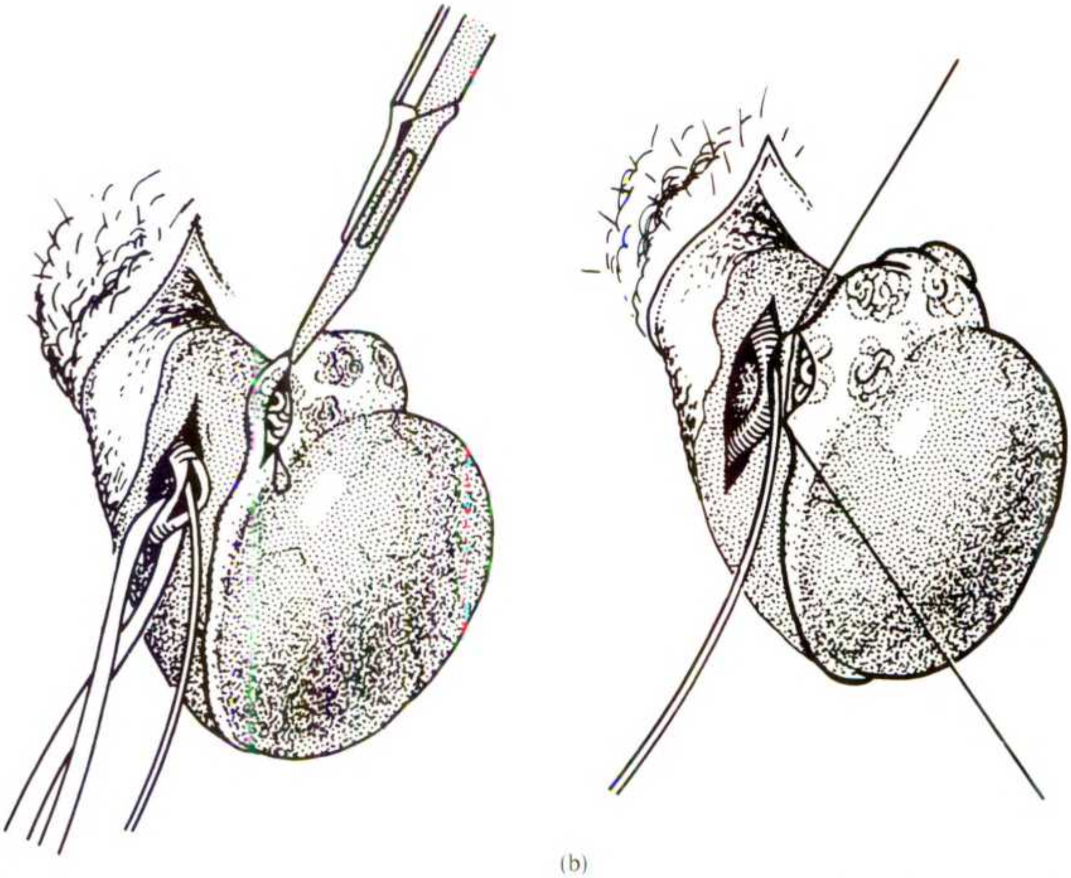

Fig. 2 (a) Vasography and (b) epididymovasostomy using 6/0 Prolene. The vasography cannula was removed after completion of the upper end of the anastomosis.

Table 2 Findings at Scrotal Exploration

Sperms in Epididymis	*Number of cases*	*Testicular biopsy*	*Past history*
Absent (Group I)	3	1. Normal 2. Maturation arrest 3. Partial atrophy	Varicocoele Prolonged pyrexia Pituitary tumour
Present (Groups II, III, IV, V)	27		

surgery: 4 ml, 13 million/ml, 5% motile; 18 months after surgery: 5 ml, 32 million/ml, 40% motile.

Case 2

Twenty-seven-year-old man said to have fathered a child in previous marriage. Avoided all fruit and vegetables, and drank $\frac{1}{4}$ - $\frac{1}{2}$ bottle of spirits 4 days a week. Sperm counts, B 12 and folate levels shown in Table 5, before and after surgery and after being seen in Haematology Clinic in December, 1977, when he was told to eat a balanced diet.

Fifteen patients had bronchiectasis (3 cases), recurrent bronchitis (7 cases) or evidence of sinusitis (5 cases). No patient had *situs inversus*. In 4 of these cases sperms appeared in the ejaculate but their number was small (up to 1 million/ml) and motility poor or absent.

Table 3 Results of Vasography in 27/30 Cases with Sperms in the Epididymis and Conclusions on Probable Cause of Obstruction

Number of cases	*Findings on Vasography*	*Probable cause of obstruction*
4	Bilateral absence	*Group II* Congenital malformation of vasa
1	Left absent, right not connected	
1	Absent lumina	
1	Cystic change	
3	Unilateral block	*Group III* Post-inflammatory
1	Normal	
16	Normal	*Groups IV & V* Unknown

Table 4 Results of Epididymovasostomy in 27/30 Cases with Sperms in the Epididymis Related to the Probable Cause of Obstruction

Cause of obstruction	*Number of cases*	*Post-operative sperm count (m/ml)*			
		0	*<1*	*1—20*	*>20*
Group II					
Congenital malformation of vasa	7	7			
Group III					
Post-inflammatory	4	3			1*
Group IV Unknown					
Bronchiectasis	3	3			
Bronchitis	7	5	2†		
Sinusitis	5	3	2†		
Group V					
? Diet deficiency	1				1*

*Normal sperm motility †Sperm motility poor or absent

Table 5 Case 2: Sperm Counts, B12 and Folate Levels Before and After Surgery and Dietary Advice (see text for details)

Date	*Sperm Count (m/ml)*	*Folate*		*B 12 (N 160—900)*
		Serum (N 4–18)	*Red Cell (N 161–640)*	
Nov 77	Azoospermia × 2	3.0*	151*	220
Nov 77	*Ep-vasostomy*			
Dec 77	Azoospermia			
Feb 78	74 m/ml	4.1	221	200
May 78	87 m/ml			

*With hypersegmented polymorphonuclear leucocytes

Respiratory Function Tests

The results of these tests will be described in detail elsewhere. No evidence of fibrocystic disease or alpha-1-antitrypsin deficiency was found in any patient. Five selected patients with chest symptoms showed significantly diminished tracheobronchial mucociliary clearance of inhaled radiolabelled particles (Fig. 3).

Pathological Findings

Histological examination of biopsies from the heads of epididymes showed dilated tubules with

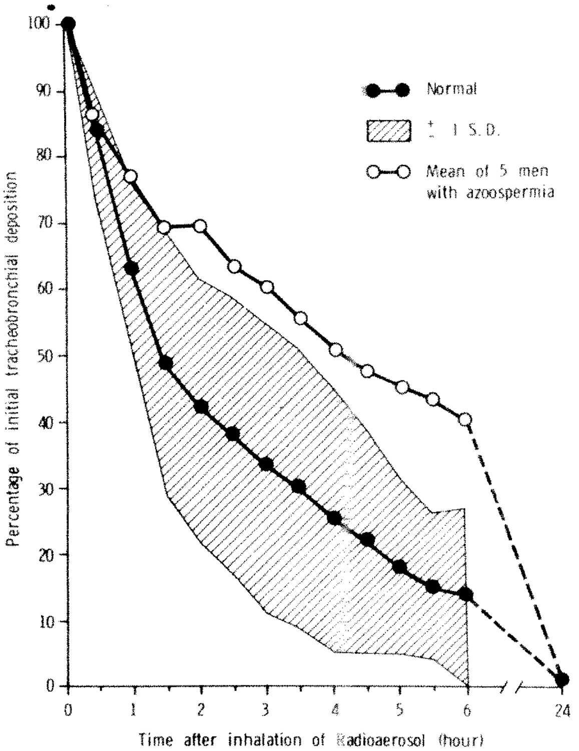

Fig. 3 Tracheobronchial clearance after inhalation of radiolabelled particles in 5 patients with chest symptoms, showing significant delay in mucociliary clearance.

normal peritubular musculature and normal ciliated epithelium in some areas, but with flattened epithelium in other areas. Some tubules contained clumps of degenerate and partially phagocytosed sperms, while others contained amorphous material and prominent cholesterol clefts. Biopsies from mid-epididymis showed that the tubules were empty. The ciliated epithelium and microvilli (or stereocilia) appeared normal. Eosinophilic refractile inclusions were noted in some nuclei in the tubular epithelium in this region in one patient with bronchitis.

Electron microscopy in the 10 patients with bronchiectasis or bronchitis showed that the normal 9 + 2 microtubular arrangement was present in cilia from all epididymes and in the 2 bronchial biopsies. Dynein arms were present in all cases. The cilia were correctly orientated in 8 cases, but incorrectly orientated in 2 patients (Fig. 4) (see Eliasson *et al.*, 1977). Epididymal sperms were too degenerate to permit accurate examination. Ejaculated sperms examined post-operatively in 2 patients with bronchitis showed normal 9 + 2 microtubular arrangement, and dynein arms were present.

Discussion

The results of vasovasostomy compare well with the collected experience reviewed by Hulka and Davis (1972). Since the surgical technique appears to have been adequate, other factors must have been more important in deciding the success or failure of epididymovasostomy.

The criteria for selection for exploration in cases with azoospermia, of large testes and normal FSH levels, as recommended by Pryor *et al.*, (1976), appear to have been satisfactory since sperms were found in the epididymis in 27 of 30 cases. One patient had a pituitary tumour, which should be anticipated, since at present there is no lower limit of normal for FSH estimation. Following exploration of the scrotum and bilateral vasography the patients were assigned to various groups according to the cause of the obstruction. We had no success with congenital abnormalities of the vas, although at least one was suitable for surgical correction. In the post-inflammatory group the presence of co-existing vasal occlusions was sought and corrected, and the successful case illustrates that at least one year should elapse before judging the result, as recommended by Schoysman (personal communication).

The association of obstructive azoospermia with sinusitis, bronchitis or bronchiectasis (Young's syndrome) was found in 15 (50%) of 30 patients. Our investigations showed that this was not due to subclinical fibrocystic disease or alpha-1-antitrypsin deficiency. There were similarities to and distinct differences from the Immotile-Cilia-Syndrome described by Eliasson *et al.*, (1977). The type of chest disease was the same, and the mucociliary clearance studies and relative immotility of ejaculated sperms after operation indicated impaired cilial function. However, there was no dextrocardia and the cilia were ultrastructurally normal. Dynein arms were present, whereas these structures, which are necessary for sperm and cilial motility, are characteristically absent in the immotile-cilia-syndrome. Finally and most importantly, the sperm transport is normal in the immotile-cilia-syndrome, but completely obstructed in Young's syndrome; the latter must, therefore, be due to a different abnormality in muco-ciliary function, the nature of which is not yet defined. However, the basic problem is most

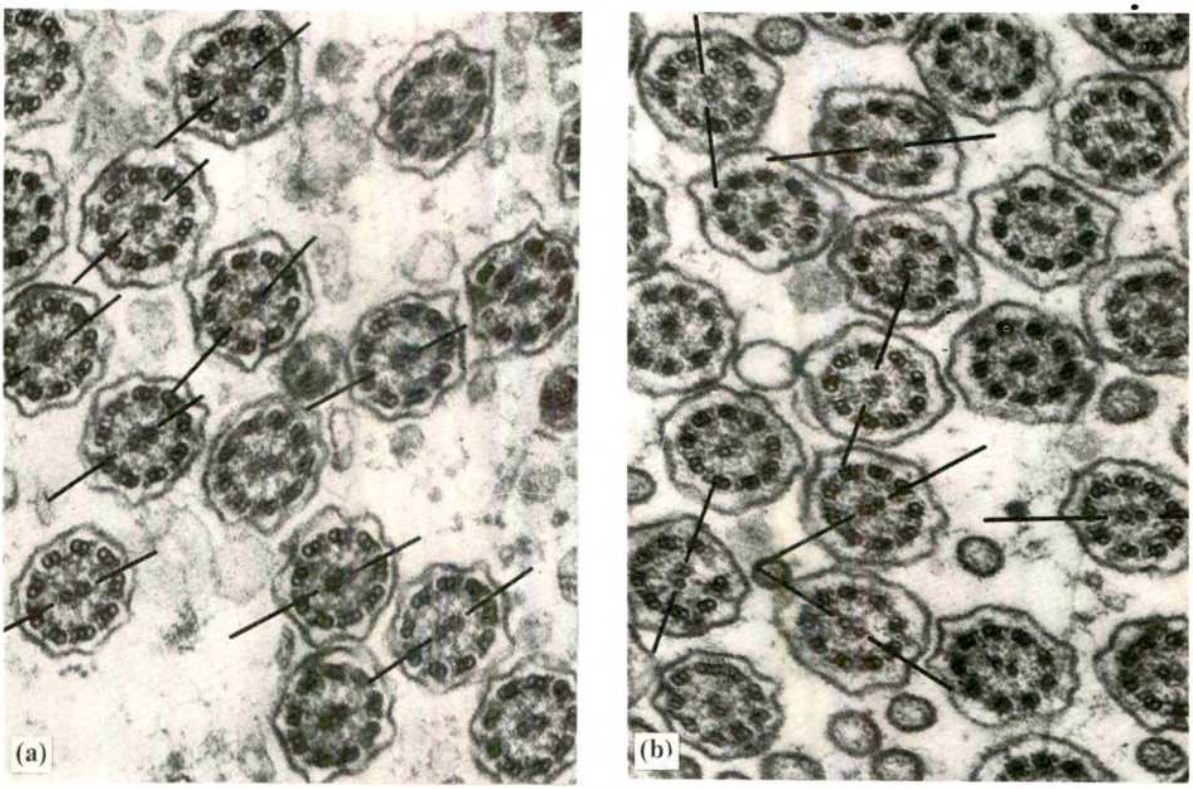

Fig. 4 (a) In 8 cases with chest disease, electron micrographs (x 60,000) of epididymal cilia showed normal 9 + 2 arrangement of microtubules, with parallel orientation of the 2 central filaments. (b) In 2 cases with chest disease electron micrographs showed abnormal orientation of the 2 central filaments.

likely to be due to malfunctioning microtubules, a condition of considerable topical interest (Lancet, 1978). Since the microtubules appear to be ultrastructurally normal in Young's syndrome, and since it is known that microtubules elsewhere can be stimulated by cyclic 3^1 5^1 – guanosine monophosphate (cyclic GMP) and cholinergic agents (Estensen *et al.,* 1973; Oliver, 1976) and by ascorbic acid (Boxer *et al*., 1976), this aspect of the disease would appear to be worthy of further study. The successful result obtained in the patient with documented dietary deficiency may indicate that reversible microtubule malfunction can be acquired, and it is possible that ascorbic acid rather than folic acid deficiency was the cause of the problem in that case. Certainly correction of the dietary deficiency may have been as responsible for the successful outcome as the surgical operation.

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The Value of Alpha-fetoprotein and Beta-human Chorionic Gonadotrophin in the Management of Testicular Tumours

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Summary—Serum alpha-fetoprotein and beta-human chorionic gonadotrophin levels were estimated in 115 patients. Sixty-nine patients had non-seminomatous germ cell tumours and 34 patients had seminomas. Twenty-six patients showed elevated serum markers.

The serum measurement of certain cancer-associated substances is useful in the diagnosis and management of cancers. The measurement of serum alpha-fetoprotein (AFP) and beta-human chorionic gonadotrophin (beta-HCG) has been shown to be valuable in the management of non-seminomatous testicular tumours (Waldmann and McIntire, 1974; Perlin *et al.*, 1976). However, the relationship of elevated AFP and beta-HCG to the histological and behavioural activity of the tumour remains an unsolved problem (Teilum *et al.*, 1975; Cochran, 1976). The cell of origin of these serum tumour markers remains uncertain. We believe that the estimation of these serum markers is useful in some testicular tumours.

Materials and Methods

Since January 1976, serum AFP and beta-HCG levels have been determined in 115 patients. The assays were by double antibody radioimmunoassay. The radioimmunoassay for AFP has a sensitivity of less than 1 ng/ml, and levels greater than 20 ng/ml are considered abnormal. The sensitivity of HCG is less than 1 ng/ml, and levels greater than 1 ng/ml are abnormal for adult males. One hundred and three patients had testicular tumours. Forty-four had been treated previously and had no evidence of metastases. Fifty-nine had untreated tumours, recent orchiectomy or evidence of metastases. Eight control patients were found to have non-malignant conditions of the scrotum, while 4 patients were suffering from stage D carcinoma of the prostate treated by orchiectomy. In 34 patients seminomas were present, and in 69 patients non-seminomatous germ cell tumours were found. All diagnoses were confirmed histologically and the presence of metastases verified both surgically and radiologically in patients with non-seminomatous germ cell tumours, and in most instances radiologically with seminomas.

Results

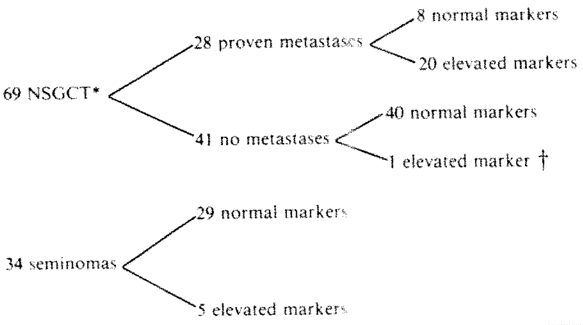
One hundred and three patients had germ cell tumours of the testis. The 44 patients with histories of previously treated testicular tumours and no evidence of metastatic disease all had normal serum markers. Of the 59 patients with untreated disease, recent orchiectomy, evidence of metastases, or recent surgical removal of their tumours, 26 showed elevated levels of AFP and/or beta-HCG (Table 1). None had any clinical or laboratory evidence of liver disease or other neoplasia that could account for elevated serum markers.

Table 1 Results of Estimation of Markers Related to Clinical Status

	No.	*No. with elevated markers*
Previously treated with no clinical evidence of tumour	44	0
Pre-orchiectomy, orchiectomised or with metastatic disease	59	26
Controls	12	0
Total	115	26

Read at the 34th Annual Meeting of the British Association of Urological Surgeons in Brighton, June 1978.

Table 2 Results of Estimation of Markers Related to Histology of Testicular Tumour and Presence or Absence of Metastases



* NSGCT = non-seminomatous germ cell tumours.
† In one patient AFP was abnormal once and later became normal without any treatment.

Histologically, 5 patients had seminoma and the other 21 had non-seminomatous germ cell testicular tumours (Table 2).

Twelve patients had elevated beta-HCG levels (Table 3). Four of these were patients with seminoma, and 5 had embryonal cell carcinoma. The remaining 3 patients had mixed tumours. Ten patients had elevated AFP. Three of these tumours were pure embryonal cell carcinomas, one seminoma, one teratocarcinoma, and the others were mixtures of various elements. Four patients had both serum markers elevated. One of these patients had embryonal cell carcinoma, another a mixture of embryonal and choriocarcinoma, and 2 embryonal cell carcinoma plus teratoma (Table 3).

All non-seminomatous germ cell testicular tumour patients with elevated serum markers had metastatic disease except one patient. This patient's investigations for metastases were negative but on one occasion showed an elevated AFP which returned to normal without any further treatment. Four patients with seminoma of the testis had elevated serum beta-HCG and one elevated AFP. All 5 were treated initially by orchiectomy plus radiation therapy. In 4 of these patients the subsequent levels of serum markers were normal. One patient's serum beta-HCG remained elevated for 4 months following completion of radiation therapy. A retroperitoneal lymphadenectomy was performed, and the microscopic examination of the nodes was normal. Subsequent serum beta-HCG levels have been within normal limits. Eight patients who had non-seminomatous germ cell tumours with retroperitoneal node metastasis did not have elevated serum markers (Table 2).

Table 3 Beta HCG and AFP Levels Related to Histology of Testicular Tumour

Histology	*Total*	*HCG*↑	*AFP*↑	*Both*↑
Seminoma	5	4	1	0
Embryonal cell Ca	9	5	3	1
Terato Ca	2	0	2	0
Embryonal + terato	6	1	3	2
Embryonal + chorio	2	1	0	1
Embryonal + seminoma	1	0	1	0
Embryonal + terato + chorio	1	1	0	0
	26	12	10	4

Eight patients with benign scrotal lesions had normal pre-operative levels of serum markers. Similarly, normal serum marker levels were obtained from 4 patients who underwent bilateral orchiectomy for stage D prostatic carcinoma.

Discussion

Alpha-fetoprotein was isolated by Bergstrand and Czar (1956) from the serum of a human fetus. It is an alpha-1-globulin, and in the early embryo is the dominant serum protein. It is replaced later by albumin. Initially the substance is produced in the human embryo first by the yolk sac and later by the liver. The highest concentration of AFP is found at about 12 to 13 weeks of gestation. Within a few weeks after birth the serum level falls rapidly to the adult level, which is very low.

In approximately 40% of patients with primary liver cancer and in mice with chemically induced hepatomas, the levels of AFP are elevated enough to be detected by gel-agar precipitation techniques (Abelev *et al.*, 1963; Abelev, 1971). The same techniques have also revealed AFP in the serum of 15 to 50% of patients with testicular or ovarian teratocarcinoma, larger percentages being found in children with such tumours (Bracken *et al.*, 1975).

By specific radioimmunoassay method, using an antibody against AFP extracted from pooled fetal plasma, Waldmann and McIntire (1974) found that approximately 70 to 80% of patients with teratocarcinoma or pure embryonal cell carcinoma of the testis had elevated serum levels. Elevated levels of AFP may also be seen in ataxia, telangiectasia and in some cases of pancreatic, biliary, gastric and other gastrointestinal neoplasms, in liver disease and in non-gastrointestinal tumour metastasis to the liver.

Human chorionic gonadotrophins are composed of 2 polypeptide subunits designated "alpha" and "beta" (Vaitukaitis *et al.*, 1972). The alpha subunits of follicle-stimulating hormone, luteinising hormone and human chorionic gonadotrophins are identical. The beta subunit is responsible for the biological activity of the hormone and differs from the alpha unit. The beta subunits of luteinising hormone and HCG are similar, and antibodies against them frequently cross-react. Recently an antibody specific for beta-HCG has been prepared so that the HCG can be measured without interference from luteinising hormone (Goldstein *et al.*, 1974). This has increased the sensitivity of the test compared to previous methods by at least 200 times. It is reported that 40 to 60% of non-seminomatous germ cell tumour patients have elevated levels of beta-HCG (Braunstein *et al.*, 1973). Increased levels are occasionally detected in patients with primary carcinoma of the pancreas, lung and kidney. Even though it is stated that abnormal AFP is associated only with embryonal cell and teratocarcinoma (Bracken *et al.*, 1975), we were unable to find this definite pattern in our cases (Table 3).

It is claimed that the serum markers are extremely sensitive pre-operative indicators of metastatic disease (Lange *et al.*, 1976). In our series 8 patients had metastatic disease in their lymph nodes, but their serum markers were within normal limits. We therefore feel that the only certain way to exclude retroperitoneal lymph node metastasis is by complete dissection of the nodes and histological examination. The normal levels of serum markers may not exclude metastatic disease.

Newlands *et al.* (1976) reported having seen 5 patients with seminoma of the testis who had elevated AFP, and 20% of their patients with seminoma showed elevated beta-HCG. We found one patient with seminoma of the testis who had elevated AFP, and 4 patients with seminoma of the testis showed elevated serum beta-HCG.

It is also reported that trophoblastic tissue elements are not essential for the production of beta-HCG (Cochran *et al.*, 1975), and our own experience prompts us to agree with this assumption. However, unless we have the opportunity to examine by step sections all the neoplastic material for evidence of trophoblastic cells both in the testicular tumour as well as the metastatic tumour, this assumption may be wrong. It is well known that the histological picture of metastatic disease may not be similar to the histological picture of primary tumour.

It is concluded that the presently accepted normal levels of serum markers may not exclude metastatic disease.

Elevated markers usually indicate active disease. However, treatment, whether by surgery, radiation and/or chemotherapy, should not be based solely on the levels of serum markers until further experience has been gained.

At the present time it is not possible to correlate the histology of the tumour and the tumour markers.

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CT Scanning and the Surgery of Metastatic Teratoma of the Testis: a Preliminary Report

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Summary—Accurate definition of metastases in para-aortic lymph nodes and lungs is essential in planning treatment for patients with testicular teratoma. The addition of CT scanning to routine investigation of these patients has given additional sensitivity in detection and localisation of metastases. The extent of para-aortic metastases could be clearly defined, even when bulk replacement of nodes prevented definition by lymphography. This information was used in planning the best surgical approach for para-aortic lymphadenectomy, which was done as part of combined treatment of large volume metastases.

The surgery of metastatic teratoma of the testis after initial orchiectomy principally comprises abdominal lymphadenectomy. The indications for abdominal lymphadenectomy vary widely between urological centres. In North America abdominal lymphadenectomy is widely advocated in patients with Stage I and Stage II (see Appendix) malignant teratoma of the testis, both as a means of eliminating metastatic tumour and to enable the tumour to be accurately staged through the identification of microscopic metastases (Skinner, 1976). This paper reviews the application of computerised tomographic scanning (CT scanning) to the surgical management of patients with malignant teratoma of the testis treated at the Royal Marsden Hospital. Previous experience at the Royal Marsden has indicated that radiotherapy is an effective treatment in patients with demonstrable small-volume lymph node involvement below the diaphragm (Stage IIA) (Tyrrell and Peckham, 1976). Abdominal lymphadenectomy is therefore reserved for those patients with large volume infradiaphragmatic lymph node involvement in whom there is a residual nodal mass after chemotherapy and radiotherapy. These patients may initially have had abdominal lymph node involvement alone, or there may have been mediastinal or lung metastases which have disappeared on treatment.

Patients and Methods

All 46 patients in this series had testicular teratomas and have been investigated using the EMI whole body scanner CT 5005. CT scans of the chest and abdomen have routinely been performed as part of the preliminary assessment unless advanced lung disease was present, when it was considered that CT scanning would provide no further significant information. The CT scan was repeated periodically to assess the response to treatment. The scans were stored on magnetic tape and were easily accessible for review. Relevant scans were recorded as hard copies on photographic film, and these were kept in the patient's notes.

An account of the physics of CT scanning is beyond the scope of this paper and has been described elsewhere (Hounsfield, 1973; Hill, 1974).

Results

The results of CT scanning are considered in relation to the abdomen, mediastinum and lungs. Comparison is made with conventional radiology and ultra-sound, where applicable.

The Abdomen

CT scanning of the abdomen was valuable for the information obtained regarding involved abdominal lymph nodes (Table 1) and liver metastases. One of the advantages of CT scanning

Table 1 The Demonstration of Abdominal Lymph Node Metastases—46 Patients

	CT scanning	*Lymphography*
Involved nodes demonstrated	18	17
Non-opacified nodes	15	—

Read at the 34th Annual Meeting of the British Association of Urological Surgeons in Brighton, June 1978.

Table 2 Volume Change Observed in Abdominal Lymph Nodes in Response to Treatment—13 Patients

Nodes disappeared	4 patients
Nodes smaller	2 patients
Nodes same size	5 patients
Nodes larger	2 patients

was the ability of CT (computerised tomography) to recognise enlarged lymph nodes that were inaccessible to lymphography. When surgery was being considered for patients with demonstrable residual nodal disease within the abdomen, it was particularly important to define the presence, size and position of the involved nodes in order to determine operability and surgical approach.

There was close agreement between lymphography and CT scanning in identifying the presence of involved abdominal lymph nodes. Only once in this series was the CT scan able to detect involved abdominal nodes when the lymphogram was negative. However, CT scanning did provide additional information regarding the extent of abdominal disease in 15 patients. The response of involved lymph nodes to treatment was of considerable importance since surgery was not performed in the absence of residual disease. Table 2 shows the changes in abdominal lymph node volume observed in patients who had sequential CT scans.

The level of involved lymph nodes in relation to the renal veins determined the surgical approach. A midline incision was judged to be adequate when node involvement lay below the renal vein (Mallis and Patton, 1958) and a thoraco-abdominal approach was employed when lymph node involvement extended above the renal veins (Skinner and Leadbetter, 1971). In the 6 patients who came to abdominal lymphadenectomy following a CT scan the approach has invariably proved to be the correct one, and in all of these patients the anatomy of the involved nodes found at operation approximated closely to the anatomy predicted from the CT scan.

Liver metastases were a contraindication to surgery. In this series liver metastases were identified by CT scanning in 3 patients in whom surgery might otherwise have been undertaken. Ultrasound also identified metastases in these 3 patients but indicated the presence of metastases in a further 2 patients in whom the CT scans were normal. These 2 patients have been followed for 9 months without treatment and have remained well throughout this time. The presence of hepatic metastases in these patients would, therefore, seem unlikely.

Lungs and Mediastinum

In this series of 46 patients, mediastinal nodes were identified by the CT scanner in 4 patients. Conventional radiology detected mediastinal nodes in only one of these patients. Lung metastases were identified by both CT scanning and whole lung tomography in 24 patients. Lung metastases were identified on the CT scan in 4 patients passed as clear using whole lung tomography, and in 13 patients greater numbers of metastases were detected using a CT scanner than were apparent on the whole lung tomograms. CT scanning, therefore, provided additional evidence of disease in one-third of the patients.

Discussion

The accuracy with which involved lymph nodes and pulmonary metastases were revealed on the CT scan was better than that achieved by ultrasound or conventional X-ray techniques. In this series of 46 patients CT has demonstrated supradiaphragmatic involvement in 7 patients passed as clear using conventional radiology. The elimination of supradiaphragmatic disease is an essential preliminary before abdominal lymphadenectomy, and this response to therapy could be accurately judged using repeated CT scanning.

Within the abdomen lymphography is an accurate method of demonstrating the presence of involved lymph nodes (Wilkinson and MacDonald, 1975). One limitation of lymphography, however, is the failure of contrast to fill nodes that are extensively involved with tumour, and hence to delineate accurately large nodal masses. The presence of involved nodes must, therefore, be inferred from the displacement of neighbouring structures, such as the kidneys and ureters. CT scanning complements lymphography by demonstrating these non-opacified lymph nodes directly, and thus enables a quantitative estimation to be made of the amount of tumour present.

In experienced hands ultra-sound has been demonstrated to be a valuable technique in the assessment of abdominal lymphadenopathy (Tyrrell *et al.*, 1977). However, difficulties may arise when the rib cage interferes with localisation of lymph nodes in the upper abdomen, and in the lower abdomen lymph nodes may be obscured by gas within the bowel. These limitations do not apply to CT scanning since the rib cage does not interfere with the image and intestinal gas interferes only when peristalsis is present; this can be largely overcome by the routine use of anticholinergic drugs.

Conclusion

These results demonstrate the advantages that are offered by CT scanning in the assessment and surgical management of patients with malignant teratoma of the testis. It is hoped that further results and future survival data will support these preliminary findings.

Appendix

Staging classification (Royal Marsden Hospital (Tyrrell *et al.*, 1977))

Stage I	Negative lymphogram, no metastases detected elsewhere.
Stage IIA	Positive lymphogram, with small volume node metastases (< 2 cm maximum diameter). No metastases elsewhere.
Stage IIB	Positive lymphogram, bulky metastases (> 2 cm maximum diameter). No metastases elsewhere.
Stage III	Nodes involved above and below diaphragm: A, small volume; B, bulky disease.
Stage IVA	Minimal lung (< 4 metastases).
Stage IVB	Advanced lung (> 4 metastases).
Stage IVC	Extrathoracic (liver, bone, brain, etc.).

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AUTHOR INDEX

Aaronson, I. A. Carcinoma in the bladder left behind, 139
Abel, B. J. and Gow, J. G. Results of caecocystoplasty for tuberculous bladder contracture, 511
Abel, B. J. and Kennedy, J. H. Severe hypertension following traumatic renal infarction, 54
Abercrombie, G. F., jt. author. *See* Vinnicombe, J.
Abrams, P. D., jt. author. *See* Cardozo, L. D.
Abrams, P. H., Martin, S. and Griffiths, D. J. The measurement and interpretation of urethral pressures obtained by the method of Brown and Wickham, 33
Abrams, P. H., jt. author. *See* Dunn, M.
Abrams, P. H., jt. author. *See* George, N. J. R.
Ahad, A., Wani, N. A., Bhan, B. L. and Garyali, R. K. Ectopia testis transversa, 215
Alberti, K. G. M. M., jt. author. *See* Foster, K. J.
Allan, V., jt. author. *See* Cardozo, L.
Allen, N. H., jt. author. *See* Foster, K. J.
Allen, N. H., jt. author. *See* Jenkins, J. D.
Alsabti, E. A. K. Serum alphafetoprotein (AFP) in bilharziasis, 134
Anderson, C. K., jt. author. *See* Stewart, P. A. H.
Anderson, C. K., jt. author. *See* Taylor, T. A.
Anikwe, R. M. Urodynamics in benign prostatic hypertrophy, 20
Appell, R. A., Bagley, D. H., Shield, D. E. and McGuire, E. J. Calyceal injury due to external ureteric compression during urography, 214
Arkell, D. G., Cotter, K. P., Fitz-Patrick, J. D. and Shaw, R. E. Pre-operative arterial embolisation in renal carcinoma, 469
Asha, H. A., jt. author. *See* Ibrahim, A.
Askew, A. R., jt. author. *See* Bishop, M. C.
Asklin, B., jt. author. *See* Pettersson, S.
Atimomo, C. An isolated injury of right renal artery due to blunt trauma, 430
Attygalle, L. S., jt. author. *See* Thavarasah, A. S.
Atwell, J. D. and Vijay, M. R. Renal growth following reimplantation of the ureters for reflux, 367
Auf, G., jt. author. *See* Ghanadian, R.
Aughey, E., jt. author. *See* Scott, R.
Awad, S. A., Downie, J. W. and Kiruluta, H. G. Alpha-adrenergic agents in urinary disorders of the proximal urethra. Part I. Sphincteric incontinence, 332
Awad, S. A., Downie, J. W. and Kiruluta, H. G. Alpha-adrenergic agents in urinary disorders of the proximal urethra. Part II. Urethral obstruction due to "sympathetic dyssynergia", 336

Bagley, D. H., jt. author. *See* Appell, R. A.
Bateman, J. R. M., jt. author. *See* Hendry, W. F.
Bayliss, A. P., jt. author. *See* Steyn, J. H.
Benakis, V., jt. author. *See* Vlahos, L.
Bennett, A. E., Jt. author. *See* Cardozo, L. D.
Beyer-Boon, M. E., Cuypers, L. H. R. I., deVoogt, H. J. and Brussee, J. A. M. Cytological changes due to urinary calculi, 81
Bhan, B. L., jt. author. *See* Ahad, A.
Bichler, K. H., jt. author. *See* Harzmann, R.
Bishop, A., jt. author. *See* Thom, J. A.
Bishop, M. C., Askew, A. R. and Smith, J. C. Reimplantation of the wide ureter, 383
Blacklock, N. J., jt. author. *See* Thom, J. A.
Blandy, J. P., jt. author. *See* Chilton, C. P.
Blandy, J. P., jt. author. *See* Gardiner, R. A.
Blandy, J. P., jt. author. *See* Glass, R. E.
Blandy, J. P., jt. author. *See* Mitchell, J. P.
Blandy, J. P., jt. author. *See* Pryor, J. P.
Blenkinsopp, W. K., jt. author. *See* Heffernan, J. C.
Boyd, P. J. R., Husband, J. E., Peckham, M. J. and Hendry, W. F. CT scanning and the surgery of metastatic teratoma of the testis: a preliminary report, 609
Braf, Z. F. and Horowitz, A. Intimal tear, cause of transplant failure, 52
Brandina, L., Mocelin, A. J., Fraga, A. M. A. and Lacerda, G. Transplantation of a horseshoe kidney, 284
Bratt, C.-G., jt. author. *See* Pettersson, S.
Bremner, D. N., jt. author. *See* Fowler, J. W.
Britton, K. E., jt. author. *See* Whitfield, H. N.
Brockis, J. G., Hulbert, J. C., Patel, A. S., Golinger, D., Hurst, P., Saker, B., Haywood, E. F., House, A. K. and Merwyk, A. Van. The diagnosis and treatment of lymphocoeles associated with renal transplantation. A report of 6 cases and a review of the literature, 307
Brocklehurst, J. C. and Brocklehurst, S. The management of indwelling catheters, 102
Brocklehurst, S., jt. author. *See* Brocklehurst, J. C.
Brown, M., jt. author. *See* Sutherst, J. R.
Brussee, J. A. M., jt. author. *See* Beyer-Boon, M. E.

Caine, M., Perlberg, S. and Meretyk, S. A placebo-controlled double-blind study of the effect of phenoxybenzamine, 551
Cameron, K. M., jt. author. *See* Pryor, J. P.
Cardozo, L. D., Abrams, P. D., Stanton, S. L., and Feneley, R. C. L. Idiopathic bladder instability treated by biofeedback, 521
Cardozo, L. D., Stanton, S. L. and Bennett, A. E. Design of a urodynamic questionnaire, 269
Cardozo, L. D., Stanton, S. L., Hafner, J. and Allan, V. Biofeedback in the treatment of detrusor instability, 250
Carroll, R. N. P., jt. author. *See* O'Reilly, P. H.
Castro, J. E., jt. author. *See* Kennedy, C. L.
Castro, J. E., jt. author. *See* Lucas, B. St. C.
Catane, R., Kaufman, J. H., Madajewicz, S., Mittelman, A. and Murphy, G. P. Prednimustine therapy for advanced prostatic cancer, 29
Chafik, M. L., jt. author. *See* Debruyne, F. M. J.
Chaput de Saintonge, D. M., jt. author. *See* Pryor, J. P.
Chilton, C. P., Morgan, R. J., England, H. R., Paris, A. M. I. and Blandy, J. P. A critical evaluation of the results of transurethral resection of the prostate, 542
Chisholm, G. D., jt. author. *See* Fitzpatrick, J. M.
Chisholm, G. D., jt. author. *See* Ghanadian, R.
Chisholm, G. D., jt. author. *See* O'Donoghue, E. P. N.

Clark, P. B. Radical cystectomy for carcinoma of the bladder, 492
Clark, P. B., jt. author. *See* Robertson, W. G.
Clark, P. B., jt. author. *See* Stewart, P. A. H.
Clark, S. S., jt. author. *See* Ray, B.
Clarke, S. W., jt. author *See* Hendry, W. F.
Collins, W. P., jt. author. *See* Pryor, J. P.
Comhaire, F., jt. author. *See* Monteyne, R.
Constable, A. R., jt. author. *See* Fitzpatrick, J. M.
Constable, A. R., jt. author. *See* O'Donoghue, E. P. N.
Contreras, F., jt. author. *See* Nistal, M.
Corbett, C. R. An unusual case of cavernositis, 53
Cotter, K. P., jt. author. *See* Arkell, D. G.
Cowie, A. G. A., jt. author. *See* Peters, J. L.
Creed, K. E. and Tulloch, A. G. S. The effect of pelvic nerve stimulation and some drugs on the urethra and bladder of the dog, 398
Culp, D. A., jt. author. *See* Loening, S.
Culp, D. A., jt. author. *See* Narayana, A. S.
Curwen, M. P., jt. author. *See* Page, B. H.
Cuypers, L. H. R. I., jt. author. *See* Beyer-Boon, M. E.

Dathan, J. R. E., jt. author. *See* Osman, J.
Davies, D. M. and Mitchell, I. Fracture of the penis, 426
Davies, P., Woods, K. A., Evans, C. M., Gray, W. M. and Kulatilake, A. E. The value of provocative and acute urography in patients with intermittent loin pain, 227
De Carvalho, H. A. A case of ureteral diverticula, 427
De Dominicis, C., jt. author. *See* Laurenti, C.
Debruyne, F. M. J., Wijdeveld, P. G. A. B., Koene, R. A. P., Chafik, M. L., Moonen, W. A. and Renders, G. A. M. Uretero-neo-cystostomy in renal transplantation: is an antireflux mechanism mandatory?, 378
Debruyne, F. M. J., jt. author. *See* Delaere, K. P. J.
Delaere, K. P. J., Debruyne, F. M. J. and Moonen, W. A. Has bromocriptine a place in the treatment of the unstable bladder?, 169
Dimopoulos, C., jt. author. *See* Vlahos, L.
Dinsdale, O., jt. author. *See* Sade, M.
Dixon, J. S., jt. author. *See* Gosling, J. A.
Dondero, F., jt. author. *See* Laurenti, C.
Dounis, A., Dunn, M. and Smith, P. J. B. Ureteric reimplantation for vesicoureteric reflux in the adult, 233
Dounis, A., jt. author. *See* Dunn, M.
Dounis, A., jt. author. *See* George, N. J. R.
Downie, J. W., jt. author. *See* Awad, S. A.
Dunn, M., Slade, N., Gumpert, J. R. W., Smith, P. J. B. and Dounis, A. The management of vesicoureteric reflux in children, 474
Dunn, M., Smith, P. J. B. and Abrams, P. H. Endoscopic examination in children, 586
Dunn, M., jt. author. *See* Dounis, A.
Dunn, M., jt. author. *See* George, N. J. R.
Dunn, M., jt. author. *See* Khezri, A. A.
Dunn, M., jt. author. *See* Smith, P. J. B.

Eckert, H., jt. author. *See* Symes, M. C.
Edwards, E. C., jt. author. *See* O'Reilly, P. H.
Edwards, L., Rosin, D., Leaper, D., Swedan, M., Trott, P. and Vertido, R. The induction of cystitis and the implantation of tumours in rat and rabbit bladders, 502
El Fahiq, A. and Wallace, D. M. Ultrasonic lithotriptor for urethral and bladder stones, 255
England, H. R., jt. author. *See* Chilton, C. P.
Evans, C. M., jt. author. *See* Davies, P.
Evans, P., jt. author. *See* Pryor, J. P.

Fagioli, A., jt. author. *See* Laurenti, C.
Fam, B. A., jt. author. *See* Whitmore, W. F.
Farr, M. J., Newling, D. W. W. and Raper, C. Simple chemotherapy for bladder lymphoma with bilateral hydronephrosis, 286
Farrar, D. J., jt. author. *See* O'Reilly, P. H.
Feneley, R. C. L., jt. author. *See* Cardozo, L. D.
Fernando, A. R., jt. author. *See* Symes, M. O.
Fernando, A. R., jt. author. *See* Wickham, J. E. A.
Firstater, M., jt. author. *See* Merimsky, E.
Fischelovitch, J. and Jancu, J. Bilateral pelvic ectopic kidneys, 51
Fitz-Patrick, J. D., jt, author. *See* Arkell, D. G.
Fitzpatrick, J. M., Constable, A. R., Sherwood, T., Stephenson, J. J., Chisholm, G. D., and O'Donoghue, E. P. N. Serial bone scanning: the assessment of treatment response in carcinoma of the prostate, 555
Fitzpatrick, J. M., jt. author. *See* Pryor, J. P.
Flamm, J., jt. author. *See* Kiesswetter, H.
Flynn, J. T., jt. author. *See* Gardiner, R. A.
Flynn, J. T., jt. author. *See* Glass, R. E.
Fossa, S. D., Sokolowski, J. and Theodorsen, L. The significance of bone marrow acid phosphatase in patients with prostatic carcinoma, 185
Foster, K. J., Alberti, K. G. M. M., Allen, N., Jenkins, J., MacIver, A., Smart, C. J. and Karran, S. J. The influence of early postoperative intravenous nutrition upon recovery after total cystectomy, 319
Fowler, J. W., Bremner, D. N. and Moffat, L. E. F. The incidence and consequences of damage to the parasympathetic nerve supply to the bladder after abdominoperineal resection of the rectum for carcinoma, 95
Fraga, A. M. A., jt. author. *See* Brandina, L.
Fraser, I., MacPherson, S. and Panagakis, A. Should patients be shaved prior to transurethral surgery?, 109
Frewen, W. K. An objective assessment of the unstable bladder of psychosomatic origin, 246
Friedberg, M., jt. author. *See* Walter, S.
Furlow, W. L. Surgical management of impotence using the inflatable penile prosthesis; experience with 103 patients, 114

Garden, N. M., jt. author. *See* Spector, M.
Gardiner, R. A., Flynn, J. T., Paris, A. M. I. and Blandy, J. P. The one-stage island patch urethroplasty, 575
Garyali, R. K., jt. author. *See* Ahad, A.
Geddes, A. M., jt. author. *See* Thomson, W. N. T.
George, N. J. R., Dunn, M., Dounis, A., Abrams, P. H. and Smith, P. J. B. The late symptomatic and functional results of enterocystoplasty, 517
Ghanadian, R., Auf, G., Chisholm, G. D. and O'Donoghue, E. P. N. Receptor proteins for androgens in prostatic disease, 567
Giannopoulos, A., jt. author. *See* Vlahos, L.

Gibbon, N. O. K., jt. author. *See* Sunder, G. S.
Giles, G. R., jt. author. *See* Modgill, V. K.
Glass, R. E., Flynn, J. T., King, J. B. and Blandy, J. P. Urethral injury and fractured pelvis, 578
Glassberg, K. I., jt. author. *See* Johnston, J. H.
Golinger, D., jt. author. *See* Brockis, J. G.
Gosling, J. A. and Dixon, J. S. Functional obstruction of the ureter and renal pelvis: a histological and electron microscopic study, 145
Gotrik, J. K., jt. author. *See* Kronborg, O.
Gow, J. G., jt. author. *See* Abel, B. J.
Gow, J. G., jt. author. *See* Mitchell, J. P.
Gow, J. G., jt author. *See* Sade, M.
Gray, W. M., jt. author. *See* Davies, P.
Gregoir, W. and Schulman, C. C. Exstrophy of the bladder: treatment by trigonosigmoidostomy—long-term results, 90
Griffiths, D. J., jt. author. *See* Abrams, P. H.
Gulati, S. M., jt. author. *See* Taneja, O. P.
Gumpert, J. R. W., jt. author. *See* Dunn, M.
Gupta, A. S., jt. author. *See* Khamesra, H. L.

Hafner, J., jt. author. *See* Cardozo, L. D.
Hager, Th., jt. author. *See* Wilhelm, E.
Hakky, S. I. A new self-retaining catheter with triple microtip pressure transducer: "The Baghdad modification", 535
Hallson, P. C. and Rose, G. A. A new urinary test for stone "activity", 442
Hargreave, T. B. and Jequier, A. M. Can follicle stimulating hormone estimation replace testicular biopsy in the diagnosis of obstructive azoospermia?, 415
Harzmann, R., Bichler, K. H. and Ideler, V. The use of pure carbon stomata (biocarbon) in urinary diversion, 485
Haywood, E. F., jt. author. *See* Brockis, J. G.
Heal, M. R., jt. author. *See* McLoughlin, G. A.
Heap, S. W., jt. author. *See* Mee, A. D.
Heffernan, J. C. and Blenkinsopp, W. K. Epididymal sarcoidosis, 211
Hendry, W. F., Knight, R. K., Whitfield, H. N., Stansfeld, A. G., Pryse-Davies, J., Ryder, T. A., Pavia, D., Bateman, J. R. M. and Clarke, S. W. Obstructive azoospermia: respiratory function tests, electron microscopy and the results of surgery, 598
Hendry, W. F., jt. author. *See* Boyd, P. J. R.
Hendry, W. F., jt. author. *See* Whitfield, H. N.
Hendry, W. F., jt. author. *See* Wickham, J. E. A.
Hening, G., jt. author. *See* Wilhelm, E.
Heyburn, P. J., jt. author. *See* Robertson, W. G.
Higson, R. H., Smith, J. C. and Whelan, P. Bladder rupture: an acceptable complication of distension therapy, 529
Hirsh, A. V., jt. author. *See* Pryor, J. P.
Horowitz, A., jt. author. *See* Braf, Z. F.
House, A. K., jt. author. *See* Brockis, J. G.
Hulbert, J. C., jt. author. *See* Brockis, J. G.
Hurst, P., jt. author. *See* Brockis, J. G.
Husband, J. E., jt. author. *See* Boyd, P. J. R.

Ibrahim, A. The relationship between urinary bilharziasis and urolithiasis in the Sudan, 294
Ibrahim, A. and Asha, H. A. Prediction of renal recovery in hydronephrotic kidneys, 222
Ideler, V., jt. author. *See* Harzmann, R.
Innes, J. A., jt. author. *See* Thomson, W. N. T.

Jackett, D. M. R., jt. author. *See* Khan, A. N.
James, E. D. The behaviour of the bladder during physical activity, 387
Jameson, R. M., jt. author. *See* Tait, I. A.
Jancu, J., jt. author. *See* Fischelovitch, J.
Jenkins, J. D., jt. author. *See* Foster, K. J.
Jenkins, J. D. and Allen, N. H. Bladder neck incision—a treatment for retention with overflow in the absence of adenoma, 395
Jenkins, J. D., jt. author. *See* Turnbull, A. R.
Jequier, A. M., jt. author. *See* Hargreave, T. B.
Johnston, J. H., Koff, S. A. and Glassberg, K. I. The pseudo-obstructed bladder in enuretic children, 505
Jones, N., jt. author. *See* Taylor, T. A.

Kambal, A., Wahab, S. M. A. and Khattas, A. H. The pattern of urolithiasis in the Sudan, 376
Karatzas, G., jt. author. *See* Vlahos, L.
Karran, S. J., jt. author. *See* Foster, K. J.
Kaufman, J. H., jt. author. *See* Catane, R.
Kawachi, J., jt. author. *See* Senoh, K.
Kaye, K. Exstrophy-variant of the bladder, 356
Kennedy, C. L., Williams, G. and Castro, J. E. Angiofollicular hamartoma of Castleman, 285
Kennedy, J. H., jt. author. *See* Abel, B. J.
Keyes, W. I., jt. author. *See* Steyn, J. H.
Khamesra, H. H., Gupta, A. S. and Malpani, N. K. Transverse testicular ectopia, 283
Khan, A. N., Lee, G. S., Jackett, D. M. R., Newcombe, R. G. and Pathy, M. S. The effect of routine digital examination of the prostate on serum acid phosphatase, 182
Khattas, A. H., jt. author. *See* Kambal, A.
Khezri, A. A., Dunn, M., Smith, P. J. B. and Mitchell, J. P. Carcinoma of the penis, 275
Kiesswetter, H. and Flamm, J. The mucosal electrosensitivity threshold (MST): a test for use in conjunction with electronic stimulation in urinary incontinence in women, 262
Kinder, C. H., jt. author. *See* Mitchell, J. P.
King, J. B., jt. author. *See* Glass, R. E.
Kiruluta, H. G., jt. author. *See* Awad, S. A.
Kiviat, M. D., jt. author. *See* Stack, G. M.
Knight, R. K., jt. author. *See* Hendry, W. F.
Koene, R. A. P., jt. author. *See* Debruyne, F. M. J.
Koff, S. A., jt. author. *See* Johnston, J. H.
Kramer, B. An unusual case of persistent renal collar in a human adult male, 157
Krarup, T. The testes after torsion, 43
Kronborg, O., Ostergaard, A., Steven, K. and Gotrik, J. K. Polyglycolic acid versus chromic catgut in bladder surgery, 324
Kulatilake, A. E., jt. author. *See* Davies, P.

Lacerda, G., jt. author. *See* Brandina, L.
Lai, T., jt. author. *See* Symes, M. O.
Laurenti, C. and De Dominicis, C. A cyst in the penis of a child, 213

Laurenti, C., Fagioli, A., Lenzi, A. and Dondero, F. Antisperm antibodies in a case of secondary unilateral testicular atrophy, 352
Lawson, R. S., jt. author. *See* O'Reilly, P. H.
Leaper, D., jt. author. *See* Edwards, L.
Lee, G. S., jt. author. *See* Khan, A. N.
Lenzi, A., jt. author. *See* Laurenti, C.
Leong, C. H., jt. author. *See* Yu, H. H. Y.
Levison, V. B., jt. author. *See* Page, B. H.
Loening, S., Narayana, A., Yoder, L., Slymen, D., Weinstein, S., Penick, G. and Culp, D. Longitudinal study of bladder cancer with cytology and biopsy, 506
Loening, S., jt. author. *See* Narayana, A. S.
Lome, L. G. Renal carcinoma in a horseshoe kidney, 142
Lovegrove, F., jt. author. *See* McGregor, B.
Lucas, B. St. C. and Castro, J. E. Calculi in renal transplants, 302

MacDonald, A. F., jt. author. *See* Steyn, J. H.
McGregor, B., Tulloch, A. G. S., Quinlan, M. F. and Lovegrove, F. The role of bone scanning in the assessment of prostatic carcinoma, 178
McGuire, E. J. Reflex urethral instability, 200
McGuire, E. J., jt. author. *See* Appell, R. A.
MacIver, A., jt. author. *See* Foster, K. J.
McLoughlin, G. A., Heal, M. R. and Tyrell, I. M. An evaluation of techniques used for the production of temporary renal ischaemia, 371
MacPherson, S., jt. author. *See* Fraser, I.
Madajewicz, S., jt. author. *See* Catane, R.
Mahony, J. D. H., jt. author. *See* Pryor, J. P.
Mahony, J. F., jt. author. *See* Savdie, E.
Malpani, N. K., jt. author. *See* Khamesra, H. L.
Marins, J. L. C., jt. author. *See* Oliveira Filho, J. A. De
Marshall, D. H., jt. author. *See* Robertson, W. G.
Martin, S., jt. author. *See* Abrams, P. H.
Mathieson, A., jt. author. *See* Scott, R.
Mayo, M. E., jt. author. *See* Stack, G. M.
Mee, A. D. and Heap, S. W. pre-operative balloon occlusion of the renal artery for radical nephrectomy, 153
Meretyk, S., jt. author. *See* Caine, M.
Merimsky, E. and Firstater, M. Ectopic thoracic kidney, 282
Merwyk, A. van, jt. author. *See* Brockis, J. G.
Milewski, P. J. Radiograph measurements and contralateral renal size in primary pelvic hydronephrosis, 289
Millard, R. J. Busulphan haemorrhagic cystitis, 210
Miller, G. D. and Slade, P. J. B. Successful pregnancy in a patient with previous ectopia vesicae, 281
Milling, M. A. P. and Santer, G. J. Renogastric fistula, 423
Milroy, E., jt. author. *See* Symes, E. K.
Milroy, E. J. G., jt. author. *See* Pengelly, A. W.
Mitchell, I., jt. author. *See* Davies, D. M.
Mitchell, J. P., Blandy, J., Gow, J. G., Kinder, C. H., Turner-Warwick, R. T. and Withycombe, J. F. R. Report of the Standing Committee on Urological Instruments: endoscopes, 361
Mitchell, J. P., jt. author. *See* Khezri, A. A.
Mitchell, J. P., jt. author. *See* Symes, M. O.
Mittelman, A., jt. author. *See* Catane, R.
Mocelin, A. J., jt. author. *See* Brandina, L.
Modgill, V. K., Wiggins, P. A. and Giles, G. R. Perfusion characteristics of preserved canine kidneys subjected to warm ischaemia, 1
Moffat, L. E. F., jt. author. *See* Fowler, J. W.
Moisey, C. U. and Rees, R. W. M. Results of transurethral resection of prostate in patients with cerebrovascular disease, 539
Molland, E. A. Prostatic adenocarcinoma with ectopic ACTH production, 358
Monteyne, R. and Comhaire, F. The thermographic characteristics of varicocele: an analysis of 65 positive registrations, 118
Moonen, W. A., jt. author. *See* Debruyne, F. M. J.
Moonen, W. A., jt. author. *See* Delaere, K. P. J.
Morgan, R. J. and Pryor, J. P. Procarbazine (Natulan) in the treatment of Peyronie's disease, 111
Morgan, R. J., jt. author. *See* Chilton, C. P.
Morris, J. E., jt. author. *See* Thom, J. A.
Munro, J. F., jt. author. *See* Thomson, W. N. T.
Murdoch, J. McC., jt. author. *See* Thomson, W. N. T.
Murphy, G. P., jt. author. *See* Catane, R.

Nakashima, K., jt. author. *See* Oka, M.
Nakashima, N., jt. author. *See* Sakoda, R.
Narayana, A. S., Loening, S. and Culp, D. A. The value of alpha-fetoprotein and beta-human chorionic gonadotrophin in the management of testicular tumours, 605
Narayana, A., jt. author. *See* Loening, S.
Newcombe, R. G., jt. author. *See* Khan, A. N.
Newling, D. W. W., jt. author. *See* Farr, M. J.
Ngan, H., jt. author. *See* Yu, H. H. Y.
Nimmon, C. C., jt. author. *See* Whitfield, H. N.
Nistal, M., Contreras, F. and Paniagua, R. Adenomatoid tumour of the epididymis: histochemical and ultrastructural study of 2 cases, 121

O'Donoghue, E. P. N., Constable, A. R., Sherwood, T., Stevenson, J. J. and Chisholm, G. D. Bone scanning and plasma phosphatases in carcinoma of the prostate, 172
O'Donoghue, E. P. N., jt. author. *See* Fitzpatrick, J. M.
O'Donoghue, E. P. N., jt. author. *See* Ghanadian, R.
Oka, M., Nakashima, K. and Sakoda, R. Congenital parameatal urethral cyst in the male, 340
Oka, M., Nakashima, K. and Sakoda, R. Torsion of the mesorchium—the testis twisted upon the epididymis, 428
Oka, M., jt. author. *See* Sakoda, R.
Oliveira Filho, J. A. De, Silveira, E. and Marins, J. L. C. Metastasis from renal carcinoma to a phalanx of the hand, 280
O'Reilly, P. H., Lawson, R. S., Shields, R. A., Testa, H. J., Edwards, E. C. and Carroll, R. N. P. A radioisotope method of assessing uretero-ureteric reflux, 164
O'Reilly, P. H., Testa, H. J., Lawson, R. S., Farrar, D. J. and Edwards, E. C. Diuresis renography in equivocal urinary tract obstruction, 76
Osada, Y., jt. author. *See* Senoh, K.
Osman, J., Regan, R. J. and Dathan, J. R. E. Bilateral renal carcinoma with metastasis in gall bladder and associated with a strongly positive ANA, 212
Ostergaard, A., jt. author. *See* Kronborg, O.

Page, B. H., Levison, V. B. and Curwen, M. P. The site of recurrence of non-infiltrating bladder tumours, 237
Panagakis, A., Smith, J. C. and Williams, J. L. One-stage excision urethroplasty for stricture, 410
Panagakis, A., jt. author. *See* Fraser, I.

Paniagua, R., jt. author. *See* Nistal, M.
Paris, A. M. I., jt. author. *See* Chilton, C. P.
Paris, A. M. I., jt. author. *See* Gardiner, R. A.
Parrott, T. S., jt. author. *See* Woodard, J. R.
Parsons, K. F., jt. author. *See* Sunder, G. S.
Patel, A. S., jt. author. *See* Brockis, J. G.
Paterson, P. J., jt. author. *See* Scott, R.
Pathy, M. S., jt. author. *See* Khan, A. N.
Pavia, D., jt. author. *See* Hendry, W. F.
Peacock, M., jt. author. *See* Robertson, W. G.
Pearson, B. S. An instrument for intrarenal irrigation, 55
Pearson, B. S. Method of mobilising the adherent obstructed ureter, 56
Peckham, M. J., jt. author. *See* Boyd, P. J. R.
Pengelly, A. W., Stephenson, T. P., Milroy, E. J. G., Whiteside, C. G. and Turner Warwick, R. T. Results of prolonged bladder distension as treatment for detrusor instability, 243
Penick, G., jt. author. *See* Loening, S.
Perlberg, S., jt. author. *See* Caine, M.
Peters, J. L. and Cowie, A. G. A. Ureteric involvement with abdominal aortic aneurysm, 313
Pettersson, S., Asklin, B. and Bratt, C.-G. Endourethral urethroplasty: a simple method for treatment of urethral strictures by internal urethrotomy and primary split skin grafting, 257
Phadke, D., jt. author. *See* Rickwood, A. M. K.
Pontifex, G., jt. author. *See* Vlahos, L.
Potvliege, P., jt. author. *See* Vandendris, M.
Poulsen, L. R., jt. author. *See* Walter, S.
Prescott, R. J., jt. author. *See* Thomson, W. N. T.
Pryor, J. P., Blandy, J. P., Evans, P., Chaput De Saintonge, D. M. and Usherwood, M. Controlled clinical trial of arginine for infertile men with oligozoospermia, 47
Pryor, J. P., Cameron, K. M., Collins, W. P., Hirsh, A. V., Mahony, J. D. H., Pugh, R. C. B. and Fitzpatrick, J. M. Indications for testicular biopsy or exploration in azoospermia, 591
Pryor, J. P., jt. author. *See* Morgan, R. J.
Pryse-Davies, J., jt. author. *See* Hendry, W. F.
Pugh, R. C. B., jt. author. *See* Pryor, J. P.

Quinlan, M. F., jt. author. *See* McGregor, B.

Raper, C., jt. author. *See* Farr, M. J.
Ray, B., Sharifi, R. and Clark, S. S. Massive scrotal and occult preputial metastases from carcinoma of the prostate, 143
Rees, D. L. P., Wickham, J. E. A. and Whitfield, H. N. Bladder instability in women with recurrent cystitis, 524
Rees, E., jt. author. *See* Tait, I. A.
Rees, R. W. M., jt. author. *See* Moisey, C. U.
Regan, R. J., jt. author. *See* Osman, J.
Renders, G. A. M., jt. author. *See* Debruyne, F. M. J.
Rickwood, A. M. K. Both ureteric orifices on the same side of the bladder, 357
Rickwood, A. M. K. Transient ureteric dilatation in neonates with imperforate anus: a report of 4 cases, 16
Rickwood, A. M. K. and Phadke, D. Pyeloplasty in infants and children with particular reference to the method of drainage post-operatively, 217
Roberts, J. B. M., jt. author. *See* Smith, P. J. B.
Roberts, J. B. M., jt. author. *See* Symes, M. O.
Robertson, W. G., Peacock, M., Heyburn, P. J., Marshall, D. H. and Clark, P. B. Risk factors in calcium stone disease of the urinary tract, 449
Rose, G. A., jt. author. *See* Hallson, P. C.
Rosin, D., jt. author. *See* Edwards, L.
Rothwell, D. L., jt. author. *See* Wallace, D. M. A.
Rous, S. N., jt. author. *See* Spector, M.
Ryder, T. A., jt. author. *See* Hendry, W. F.

Sade, M., Saverymuttu, I., Dinsdale, O. and Gow, J. G. The management of azoospermia, 595
Saha, S. K. Cordopexy: a new approach to the undescended testis, 39
Saker, B., jt. author. *See* Brockis, J. G.
Sakoda, R., Oka, M. and Nakashima, K. Leukoplakia of the penis—bleomycin treatment, 355
Sakoda, R., jt. author. *See* Oka, M.
Santer, G. J., jt. author. *See* Milling, M. A. P.
Savdie, E., Mahony, J. F. and Storey, B. G. Control of bleeding after renal biopsy with epsilonamino-caproic acid, 8
Saverymuttu, I., jt. author. *See* Sade, M.
Schulman, C. C., jt. author. *See* Gregoir, W.
Schulman, C. C., jt. author. *See* Vandendris, M.
Scott, D. G., jt. author. *See* Taylor, T. A.
Scott, R. and Aughey, E. Methyl cholanthrene and cadmium induced changes in rat prostate, 25
Scott, R., Paterson, P. J., Mathieson, A., and Smith, M. The effect of allopurinol on urinary oxalate excretion in stone formers, 455
Senoh, K., Osada, Y. and Kawachi, J. Spermatic cord liposarcoma, 429
Sharifi, R., jt. author, *See* Ray, B.
Shafik, A. Absent dartos, 354
Shaw, R. E., jt. author. *See* Arkell, D. G.
Sherwood, T., jt. author. *See* Fitzpatrick, J. M.
Sherwood, T., jt. author. *See* O'Donoghue, E. P. N.
Shield, D. E., jt. author. *See* Appell, R. A.
Shields, R. A., jt. author. *See* O'Reilly, P. H.
Sigel, A., jt. author. *See* Wilhelm, E.
Silveira, E., jt. author. *See* Oliveira Filho, J. A. De
Sinha, A. P. Neoplasms of tunica vaginalis, 424
Slade, N., jt. author. *See* Dunn, M.
Slade, P. J. B., jt. author. *See* Miller, G. D.
Slymen, D., jt. author. *See* Loening, S.
Smart, C. J., jt. author. *See* Foster, K. J.
Smart, C. J., jt. author. *See* Turnbull, A. R.
Smith, J. C., jt. author. *See* Bishop, M. C.
Smith, J. C., jt. author. *See* Higson, R. H.
Smith, J. C., jt. author. *See* Panagakis, A.
Smith, M., jt. author. *See* Scott, R.
Smith, P. J. B., Roberts, J. B. M. and Dunn, M. Coagulum pyelolithotomy, 298
Smith, P. J. B., Roberts, J. B. M. and Dunn, M. Late results of skin inlay urethroplasty, 570
Smith, P. J. B., jt. author. *See* Dounis, A.
Smith, P. J. B., jt. author. *See* Dunn, M.
Smith, P. J. B, jt. author. *See* George, N. J. R.
Smith, P. J. B., jt. author. *See* Khezri, A. A.
Sokolowski, J., jt. author. *See* Fossa, S. D.

Soni, N., jt. author. *See* Ward, A.

Spector, M., Garden, N. M. and Rous, S. N. Ultrastructure and pathogenesis of human urinary calculi, 12

Stack, G. M., Mayo, M. E. and Kiviat, M. D. Foreign body migrating to the kidney, 209

Stansfeld, A. G., jt. author. *See* Hendry, W. F.

Stanton, S. L., jt. author. *See* Cardozo, L. D.

Stephenson, J. J., jt. author. *See* Fitzpatrick, J. M.

Stephenson, T. P., jt. author. *See* Pengelly, A. W.

Steven, K., jt. author. *See* Kronborg, O.

Stevenson, J. J., jt. author. *See* O'Donoghue, E. P. N.

Stewart, P. A. H., Anderson, C. K., Williams, R. E. and Clark, P. B. Urethral tumours, 583

Stewart, P. A. H., jt. author. *See* Taylor, T. A.

Steyn, J. H., MacDonald, A. F., Keyes, W. I., Bayliss, A. P. and Towler, J. M. An assessment of computerised isotopic renal section scanning, 437

Storey, B. G., jt. author. *See* Savdie, E.

Sunder, G. S., Parsons, K. F. and Gibbon, N. O. K. Outflow obstruction in neuropathic bladder dysfunction: the neuropathic urethra, 190

Sutherst, J. R. and Brown, M. The effect on the bladder pressure of sudden entry of fluid into the posterior urethra, 406

Swedan, M., jt. author. *See* Edwards, L.

Symes, E. K. and Milroy, E. An experimental approach to the optimum oestrogen dosage in prostatic carcinoma, 562

Symes, M. O., Eckert, H., Feneley, R. C. L., Lai, T., Mitchell, J. P., Roberts, J. B. M. and Tribe, C. R. Adoptive immunotherapy and radiotherapy in the treatment of urinary bladder cancer, 328

Tagore, N. K., jt. author. *See* Taneja, O. P.

Tagore, V., jt. author. *See* Taneja, O. P.

Taneja, O. P., Tagore, N. K., Tagore, V. and Gulati, S. M. Recanalisation of vas after vasectomy: evaluation of various techniques in dogs, 342

Tait, I. A., Rees, E. and Jameson, R. M. Urethral syndrome associated with chlamydial infection of the urethra and cervix, 425

Taylor, T. A., Scott, D. G., Anderson, C. K., Jones, N. and Stewart, P. A. H. Immunological studies of testicular tissue in oligozoospermic and azoospermic patients, 419

Testa, H. J., jt. author. *See* O'Reilly, P. H.

Thavarasah, A. S., and Attygalle, L. S. Inversion of the urinary bladder, 353

Theodorsen, L., jt. author. *See* Fossa, S. D.

Thom, J. A., Morris, J. E., Bishop, A. and Blacklock, N. J. The influence of refined carbohydrate on urinary calcium excretion, 459

Thomson, W. N. T., Innes, J. A., Munro, J. F., Geddes, A. M., Prescott, J. R. and Murdoch, J. McC. Renal mobility in women attending a pyelonephritis clinic and in controls, 73

Towler, J. M. and Valerio, D. Dicynene in transurethral resection of the prostate, 547

Towler, J. M., jt. author. *See* Steyn, J. H.

Tribe, C. R., jt. author. *See* Symes, M. O.

Trott, P., jt. author. *See* Edwards, L.

Tulloch, A. G. S., jt author. *See* Creed, K. E.

Tulloch, A. G. S., jt. author. *See* McGregor, B.

Turnbull, A. R., Smart, C. J. and Jenkins, J. D. Delayed rupture of the bladder, 162

Turner Warwick, R. T., jt. author. *See* Mitchell, J. P.

Turner Warwick, R. T., jt. author. *See* Pengelly, A. W.

Tyrell, I. M., jt. author. *See* McLoughlin, G. A.

Usherwood, M., jt. author. *See* Pryor, J. P.

Valerio, D., jt. author. *See* Towler, J. M.

Vandendris, M., Schulman, C. C. and Potvliege, P. Bilateral ureteric obstruction secondary in reticulum cell sarcoma, 136

Vejlsgaard, R., jt. author. *See* Walter, S.

Vertido, R., jt. author. *See* Edwards, L.

Vijay, M. R., jt. author. *See* Atwell, J. D.

Vinnicombe, J. and Abercrombie, G. F. Total cystectomy—a review, 488

Vlahos, L., Karatzas, G., Giannopoulos, A., Benakis, V., Dimopoulos, C. and Pontifex, G. Visualisation of the lymphatics of the vulva and scrotum by direct intratissue injection of the dye, 205

Voogt, H. J. De, jt. author. *See* Beyer-Boon, M. E.

Wahab, S. M. A., jt. author. *See* Kambal, A.

Wallace, D. M., jt. author. *See* El Fahiq, S.

Wallace, D. M. A., Rothwell, D. L. and Williams, D. Innes. The long-term follow-up of surgically treated vesicoureteric reflux, 479

Walters, S. and Vejisgaard, R. Diagnostic catheterisation and bacteriuria in women with urinary incontinence, 106

Walter, S., Poulsen, L. R., Friedberg, M. and Vejlsgaard, R. The influence of wound drainage on the infection rate in kidney transplant patients, 160

Wani, N. A., jt. author. *See* Ahad, A.

Ward, A. and Soni, N. An unusual presentation of renal carcinoma, 141

Watkinson, L. E., jt. author. *See* Wickham, J. E. A.

Weinstein, S., jt. author. *See* Loening, S.

Wesolowski, S. Ureteric stricture after vaginal ureterolithotomy, 137

Wesolowski, S. Ureterosigmoidostomy (Coffey): 30-year follow-up, 138

Whelan, P., jt. author. *See* Higson, R. H.

Whiteside, C. G., jt. author. *See* Pengelly, A. W.

Whitfield, H. N., Britton, K. E., Hendry, W. F., Nimmon, C. C. and Wickham, J. E.A. The distinction between obstructive uropathy and nephropathy by radioisotope transit times, 433

Whitfield, H. N., jt. author. *See* Hendry, W. F.

Whitfield, H. N., jt. author. *See* Rees, D. L. P.

Whitfield, H. N., jt. author. *See* Wickham, J. E. A.

Whitmore, W. F., Fam, B. A., and Yalla, S. V. Experience with anteromedian (12 o'clock) external urethral sphincterotomy in 100 male subjects with neuropathic bladders, 99

Wickham, J. E. A., Fernando, A. R., Hendry, W. F., Watkinson, L. E. and Whitfield, H. N. Inosine: clinical results of ischaemic renal surgery, 465

Wickham, J. E. A., jt. author. *See* Rees, D. L. P.

Wickham, J .E. A., jt. author. *See* Whitfield, H. N.

Wiggins, P. A., jt. author. *See* Modgill, V. K.

WIJDEVELD, P. G. A. B., jt. author. *See* DEBRUYNE, F. M. J.
WILHELM, E., SIGEL, A., HAGER, TH. and HENING, G. Technique and results of the colonic conduit, continent by means of a new magnetic stoma seal: an experimental study, 264
WILLIAMS, D. INNES, jt. author. *See* WALLACE, D. M. A.
WILLIAMS, G., jt. author. *See* KENNEDY, C. L.
WILLIAMS, J. L., jt. author. *See* PANAGAKIS, A.
WILLIAMS, R. E., jt. author. *See* STEWART, P. A. H.
WITHYCOMBE, J. F. R., jt. author. *See* MITCHELL, J. P.
WOODARD, J. R. and PARROTT, T. S. Orchipexy in the prune belly syndrome, 348
WOODS, K. A., jt. author. *See* DAVIES, P.

YALLA, S. V., jt. author. *See* WHITMORE, W. F.
YIM, C. M., jt. author. *See* YU, H. H. Y.
YODER, L., jt. author. *See* LOENING, S.
YU, H. H. Y., NGAN, H. and LEONG, C. H. Chyluria—a 10-year follow-up, 126
YU, H. H. Y., YIM, C. M. and LEONG, C. H. Primary actinomycosis of kidney presenting with reno-colic fistula, 140

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CONTENTS

ORIGINAL ARTICLES

PAGE

Perfusion Characteristics of Preserved Canine Kidneys subjected to Warm Ischaemia. By V. K. Modgill, P. A. Wiggins and G. R. Giles 1

Control of Bleeding after Renal Biopsy with Epsilonamino-Caproic Acid. By E. Savdie, J. F. Mahony and B. G. Storey 8

Ultrastructure and Pathogenesis of Human Urinary Calculi. By M. Spector, N. M. Garden and S. N. Rous 12

Transient Ureteric Dilatation in Neonates with Imperforate Anus: a Report of 4 Cases. By A. M. K. Rickwood 16

Urodynamics in Benign Prostatic Hypertrophy. By R. M. Anikwe 20

Methyl Cholanthrene and Cadmium Induced Changes in Rat Prostate. By R. Scott and E. Aughey 25

Prednimustine Therapy for Advanced Prostatic Cancer. By R. Catane, J. H. Kaufman, S. Madajewicz, A. Mittelman and G. P. Murphy 29

The Measurement and Interpretation of Urethral Pressures obtained by the Method of Brown and Wickham. By P. H. Abrams, S. Martin and D. J. Griffiths 33

Cordopexy: a New Approach to the Undescended Testis. By S. K. Saha 39

The Testes aft Torsion. By Torben Krarup 43

Controlled Clinical Trial of Arginine for Infertile Men with Oligozoospermia. By J. P. Pryor, J. P. Blandy, P. Evans, D. M. Chaput De Saintonge and M. Usherwood 47

Renal Mobility in Women Attending a Pyelonephritis Clinic and in Controls. By W. N. T. Thomson, J. A. Innes, J. F. Munro, A. M. Geddes, R. J. Prescott and J. McC. Murdoch 73

Diuresis Renography in Equivocal Urinary Tract Obstruction. By P. H. O'Reilly, H. J. Testa, R. S. Lawson, D. J. Farrar and E. Charlton Edwards 76

Cytological Changes due to Urinary Calculi. By M. E. Beyer-Boon, L. H. R. I. Cuypers, H. J. de Voogt and J. A. M. Brussee 81

Exstrophy of the Bladder: Treatment by Trigonosigmoidostomy—Long-term Results. By W. Gregoir and C. C. Schulman 90

The Incidence and Consequences of Damage to the Parasympathetic Nerve Supply to the Bladder after Abdominoperineal Resection of the Rectum for Carcinoma. By J. W. Fowler, D. N. Bremner and L. E. F. Moffat 95

Experience with Anteromedian (12 O'Clock) External Urethral Sphincterotomy in 100 Male Subjects with Neuropathic Bladders. By W. F. Whitmore, III, B. A. Fam and S. V. Yalla 99

The Management of Indwelling Catheters. By J. C. Brocklehurst and Susan Brocklehurst 102

Diagnostic Catheterisation and Bacteriuria in Women with Urinary Incontinence. By Steen Walter and René Vejlsgaard 106

Should Patients be Shaved Prior to Transurethral Surgery? By Ian Fraser, Symon MacPherson and Angelos Panagakis 109

Procarbazine (Natulan) in the Treatment of Peyronie's Disease. By R. J. Morgan and J. P. Pryor 111

Surgical Management of Impotence using the Inflatable Penile Prosthesis: Experience with 103 Patients. By William L. Furlow 114

The Thermographic Characteristics of Varicocele: An Analysis of 65 Positive Registrations. By Reginald Monteyne and Frank Comhaire 118

Adenomatoid Tumour of the Epididymis: Histochemical and Ultrastructural Study of 2 Cases. By Manuel Nistal, Félix Contreras and Ricardo Paniagua 121

Chyluria—a 10-year Follow-up. By Henry H. Y. Yu., Henry Ngan and C. H. Leong 126

Serum Alphafetoprotein (AFP) in Bilharziasis. By Elias A. K. Alsabti 134

Pyeloplasty in Infants and Children with Particular Reference to the Method of Drainage Post-operatively. By A. M. K. Rickwood and D. Phadke 217

Prediction of Renal Recovery in Hydronephrotic Kidneys. By Ahmed Ibrahim and Hassan Abu Asha 222

The Value of Provocative and Acute Urography in Patients with Intermittent Loin Pain. By P. Davies, K. A. Woods, C. M. Evans, W. M. Gray and A. E. Kulatilake 227

Ureteric Reimplantation for Vesico-Ureteric Reflux in the Adult. By A. Dounis, M. Dunn and P. J. B. Smith 233

ORIGINAL ARTICLES—*continued*

PAGE

The Site of Recurrence of Non-Infiltrating Bladder Tumours. By B. H. Page, V. B. Levison and M. P. Curwen 237

Results of Prolonged Bladder Distension as Treatment for Detrusor Instability. By A. W. Pengelly, T. P. Stephenson, E. J. G. Milroy, C. G. Whiteside and R. T. Turner-Warwick 243

An Objective Assessment of the Unstable Bladder of Psychosomatic Origin. By W. K. Frewen 246

Biofeedback in the Treatment of Detrusor Instability. By L. Cardozo, S. L. Stanton, J. Hafner and V. Allan 250

Ultrasonic Lithotriptor for Urethral and Bladder Stones. By Salah El Fahiq and D. M. Wallace 255

Endourethral Urethroplasty: A Simple Method for Treatment of Urethral Strictures by Internal Urethrotomy and Primary Split Skin Grafting. By Silas Pettersson, Bjorn Asklin and Claes-Goran Bratt 257

The Mucosal Electrosensitivity Threshold (MST): A Test for use in Conjunction with Electronic Stimulation in Urinary Incontinence in Women. By H. Kiesswetter and J. Flamm 262

Technique and Results of the Colonic Conduit, Continent by Means of a New Magnetic Stoma Seal: An Experimental Study. By E. Wilhelm, A. Sigel, Th. Hager and G. Hening 264

Design of a Urodynamic Questionnaire. By Linda Cardozo, Stuart L. Stanton and A. E. Bennett 269

Carcinoma of the Penis. By A. A. Khezri, M. Dunn, P. J. B. Smith and J. P. Mitchell 275

Radiograph Measurements and Contralateral Renal Size in Primary Pelvic Hydronephrosis. By P. J. Milewski 289

The Relationship Between Urinary Bilharziasis and Urolithiasis in the Sudan. By A. Ibrahim 294

Coagulum Pyelolithotomy. By P. J. B. Smith, J. B. M. Roberts and M. Dunn 298

Calculi in Renal Transplants. By B. St. C. Lucas and J. E. Castro 302

The Diagnosis and Treatment of Lymphocoeles Associated with Renal Transplantation. A report of 6 cases and a review of the literature. By J. G. Brockis, J. C. Hulbert, A. S. Patel, D. Golinger, P. Hurst, B. Saker, E. F. Haywood, A. K. House and A. van Merwyk 307

Ureteric Involvement with Abdominal Aortic Aneurysm. By J. L. Peters and A. G. A. Cowie 313

The influence of Early Post-Operative Intravenous Nutrition upon Recovery after Total Cystectomy. By K. J. Foster, K. G. M. M. Alberti, N. Allen, J. Jenkins, A. MacIver, C. J. Smart and S. J. Karran 319

Polyglycolic Acid Versus Chromic Catgut in Bladder Surgery. By O. Kronborg, A. Ostergaard, K. Steven and J. K. Gotrik 324

Adoptive Immunotherapy and Radiotherapy in the treatment of Urinary Bladder Cancer. By M. O. Symes, H. Eckert, R. C. L. Feneley, Teresa Lai, J. P. Mitchell, J. B. M. Roberts and C. R. Tribe 328

Alpha-Adrenergic Agents in Urinary Disorders of the Proximal Urethra: Part I. Sphincteric Incontinence. By S. A. Awad, J. W. Downie and H. G. Kiruluta 332

Alpha-Adrenergic Agents in Urinary Disorders of the Proximal Urethra: Part II. Urethral Obstruction due to "Sympathetic Dyssynergia". By S. A. Awad, J. W. Downie and H. G. Kiruluta 336

Congenital Parameatal Urethral Cyst in the Male. By M. Oka, K. Nakashima and R. Sakoda 340

Recanalisation of Vas after Vasectomy. Evaluation of Various Techniques in Dogs. By O. P. Taneja, N. K. Tagore, V. Tagore and S. M. Gulati 342

Orchipexy in the Prune Belly Syndrome. By John R. Woodard and Thomas S. Parrott 348

Report of the Standing Committee on Urological Instruments: Endoscopes. By J. P. Mitchell, J. Blandy, J. G. Gow, C. H. Kinder, R. T. Turner-Warwick and J. F. R. Withycombe 361

Renal Growth Following Reimplantation of the Ureters for Reflux. By J. D. Atwell and M. R. Vijay 367

An Evaluation of Techniques Used for the Production of Temporary Renal Ischaemia. By G. A. McLoughlin, M. R. Heal and I. M. Tyrell 371

The Pattern of Urolithiasis in the Sudan. By A. Kambal, S. M. A. Wahab and A. H. Khattas 376

Uretero-Neo-Cystostomy in Renal Transplantation. Is an Antireflux Mechanism Mandatory? By F. M. J. Debruyne, P. G. A. B. Wijdeveld, R. A. P. Koene, M. L. Chafik, W. A. Moonen and G. A. M. Renders 378

ORIGINAL ARTICLES—*continued*

PAGE
Reimplantation of the Wide Ureter. By M. C. BISHOP, A. R. ASKEW and J. C. SMITH 383
The Behaviour of the Bladder During Physical Activity. By E. D. JAMES 387
Bladder Neck Incision—a Treatment for Retention with Overflow in the Absence of Adenoma. By J. D. JENKINS and N. H. ALLEN 395
The Effect of Pelvic Nerve Stimulation and Some Drugs on the Urethra and Bladder of the Dog. By K. E. CREED and A. G. S. TULLOCH 398
The Effect on the Bladder Pressure of Sudden Entry of Fluid into the Posterior Urethra. By J. R. SUTHERST and M. BROWN 406
One-stage Excision Urethroplasty for Stricture. By A. PANAGAKIS, J. C. SMITH and J. L. WILLIAMS 410
Can Follicle Stimulating Hormone Estimation Replace Testicular Biopsy in the Diagnosis of Obstructive Azoospermia? By T. B. HARGREAVE and A. M. JEQUIER 415
Immunological Studies of Testicular Tissue in Oligozoospermic and Azoospermic Patients. By T. A. TAYLOR, D. G. SCOTT, C. K. ANDERSON, N. JONES and P. A. H. STEWART 419
The Distinction between Obstructive Uropathy and Nephropathy by Radioisotope Transit Times. By H. N. WHITFIELD, K. E. BRITTON, W. F. HENDRY, C. C. NIMMON and J. E. A. WICKHAM 433
An Assessment of Computerised Isotopic Renal Section Scanning. By J. H. STEYN, A. F. MACDONALD, W. I. KEYES, A. P. BAYLISS and J. M. TOWLER 437
A New Urinary Test for Stone "Activity". By P. C. HALLSON and G. ALAN ROSE 442
Risk Factors in Calcium Stone Disease of the Urinary Tract. By W. G. ROBERTSON, M. PEACOCK, P. J. HEYBURN, D. H. MARSHALL and P. B. CLARK 449
The Effect of Allopurinol on Urinary Oxalate Excretion in Stone Formers. By R. SCOTT, P. J. PATERSON, A. MATHIESON, and M. SMITH 455
The Influence of Refined Carbohydrate on Urinary Calcium Excretion. By J. A. THOM, J. E. MORRIS, A. BISHOP and N. J. BLACKLOCK 459
Inosine: Clinical Results of Ischaemic Renal Surgery. By J. E. A. WICKHAM, A. R. FERNANDO, W. F. HENDRY, L. E. WATKINSON and H. N. WHITFIELD 465
Pre-operative Arterial Embolisation in Renal Carcinoma. By D. G. ARKELL, K. PAULE COTTER, J. D. FITZ-PATRICK and R. E. SHAW 469
The Management of Vesicoureteric Reflux in Children. By M. DUNN, N. SLADE, J. R. W. GUMPERT, P. J. B. SMITH and A. DOUNIS 474
The Long-term Follow-up of Surgically Treated Vesicoureteric Reflux. By D. M. A. WALLACE, D. L. ROTHWELL and D. I. WILLIAMS 479
The Use of Pure Carbon Stomata (Biocarbon) in Urinary Diversion. By R. HARZMANN, K. H. BICHLER and V. IDELER 485
Total Cystectomy—A Review. By J. VINNICOMBE and G. F. ABERCROMBIE 488
Radical Cystectomy for Carcinoma of the Bladder. By P. B. CLARK 492
Longitudinal Study of Bladder Cancer with Cytology and Biopsy. By S. LOENING, A. NARAYANA, L. YODER, D. SLYMEN, S. WEINSTEIN, G. PENICK and D. CULP 506
The Induction of Cystitis and the Implantation of Tumours in Rat and Rabbit Bladders. By L. EDWARDS, D. ROSIN, D. LEAPER, M. SWEDAN, P. TROTT and R. VERTIDO 502
The Pseudo-obstructed Bladder in Enuretic Children. By J. H. JOHNSTON, S. A. KOFF and K. I. GLASSBERG 505
Results of Caecocystoplasty for Tuberculous Bladder Contracture. By B. J. ABEL and J. G. GOW 511
The Late Symptomatic and Functional Results of Enterocystoplasty. By N. J. R. GEORGE, M. DUNN, A. DOUNIS, P. H. ABRAMS and P. J. B. SMITH 517
Idiopathic Bladder Instability Treated by Biofeedback. By LINDA D. CARDOZO, P. D. ABRAMS, S. L. STANTON and R. C. L. FENELEY 521
Bladder Instability in Women with Recurrent Cystitis. By D. L. P. REES, J. E. A. WICKHAM and H. N. WHITFIELD 524
Bladder Rupture: An Acceptable Complication of Distension Therapy. By R. H. HIGSON, J. C. SMITH and P. WHELAN 529
A New Self-Retaining Catheter with Triple Microtip Pressure Transducer: "The Baghdad Modification". By S. I. HAKKY 535
Results of Transurethral Resection of Prostate in Patients with Cerebrovascular Disease. By C. U. MOISEY and R. W. M. REES 539
A Critical Evaluation of the Results of Transurethral Resection of the Prostate. By C. P. CHILTON, R. J. MORGAN, H. R. ENGLAND, A. M. I. PARIS and J. P. BLANDY 542

ORIGINAL ARTICLES—*continued* PAGE

Dicynene in Transurethral Resection of the Prostate. By J. M. Towler and D. Valerio 547
A Placebo-controlled Double-blind Study of the Effect of Phenoxybenzamine in Benign Prostatic Obstruction. By M. Caine, S. Perlberg and S. Meretyk 551
Serial Bone Scanning: The Assessment of Treatment Response in Carcinoma of the Prostate. By J. M. Fitzpatrick, A. R. Constable, T. Sherwood, J. J. Stephenson, G. D. Chisholm and E. P. N. O'Donoghue 555
An Experimental Approach to the Optimum Oestrogen Dosage in Prostatic Carcinoma. By Elizabeth K. Symes and E. Milroy 562
Receptor Proteins for Androgens in Prostatic Disease. By R. Ghanadian, G. Auf, G. D. Chisholm and E. P. N. O'Donoghue 567
Late Results of Skin Inlay Urethroplasty. By P. J. B. Smith, J. B. M. Roberts and M. Dunn 570
The One-stage Island Patch Urethroplasty. By R. A. Gardiner, J. T. Flynn, A. M. I. Paris and J. P. Blandy 575
Urethral Injury and Fractured Pelvis. By R. E. Glass, J. T. Flynn, J. B. King and J. P. Blandy 578
Urethral Tumours. By P. A. Hamilton Stewart, C. K. Anderson, R. E. Williams and P. B. Clark 583
Endoscopic Examination in Children. By M Dunn, P. J. B. Smith and P. H. Abrams 586
Indications for Testicular Biopsy or Exploration in Azoospermia. By J. P. Pryor, K. M. Cameron, W. P. Collins, A. V. Hirsh, J. D. H. Mahony, R. C. B. Pugh and J. M. Fitzpatrick 591
The Management of Azoospermia. By M. Sade, Indira Saverymuttu, Olive Dinsdale and J. G. Gow 595
Obstructive Azoospermia: Respiratory Function Tests, Electron Microscopy and the Results of Surgery. By W. F. Hendry, R. K. Knight, H. N. Whitfield, A. G. Stansfeld, J. Pryse-Davies, T. A. Ryder, D. Pavia, J. R. M. Bateman and S. W. Clarke 598
The Value of Alpha-fetoprotein and Beta-human Chorionic Gonadotrophin in the management of Testicular Tumours. By A. S. Narayana, S. Loening and D. A. Culp 605
CT Scanning and the Surgery of Metastatic Teratoma of the Testis: a Preliminary Report. By P. J. R. Boyd, J. E. Husband, M. J. Peckham and W. F. Hendry 609

CASE REPORTS

Bilateral Pelvic Ectopic Kidneys. By J. Fischelovitch and J. Jancu 51
Intimal Tear, cause of Transplant Failure. By Zvi F. Braf and Ada Horowitz 52
An Unusual Case of Cavernositis. By C. R. Corbett 53
Severe Hypertension following Traumatic Renal Infarction. By B. J. Abel and J. H. Kennedy 54
Bilateral Ureteric Obstruction Secondary in Reticulum Cell Sarcoma. By M. Vandendris, C. C. Schulman and P. Potvliege 136
Ureteric Stricture after Vaginal Ureterolithotomy. By Stefan Wesolowski 137
Ureterosigmoidostomy (Coffey): 30-year Follow-up. By Stefan Wesolowski 138
Carcinoma in the Bladder Left Behind. By Ian A. Aaronson 139
Primary Actinomycosis of Kidney Presenting with Reno-colic Fistula. By H. H. Y. Yu, C. M. Yim and C. H. Leong 140
An Unusual Presentation of Renal Carcinoma. By Anthony Ward and Neil Soni 141
Renal Carcinoma in a Horseshoe Kidney. By Leon G. Lome 142
Massive Scrotal and Occult Preputial Metastases from Carcinoma of the Prostate. By Biswanay Ray, Roohollah Sharifi and Samuel S. Clark 143
Metastasis from Renal Carcinoma to a Phalanx of the Hand. By J. A. de Oliveira Filho, W. Silveira and J. L. C. Marins 280
Successful Pregnancy in a Patient with Previous Ectopia Vesicae. By G. D. Miller and P. J. B. Slade 281
Ectopic Thoracic Kidney. By E. Merimsky and M. Firstater 282
Transverse Testicular Ectopia. By H. L. Khamesra, A. S. Gupta and N. K. Malpani 283
Transplantation of a Horseshoe Kidney. By L. Brandina, A. J. Mocelin, A. M. A. Fraga and G. Lacerda 284
Angiofollicular Hamartoma of Castleman. By C. L. Kennedy, G. Williams and J. E. Castro 285
Simple Chemotherapy for Bladder Lymphoma with Bilateral Hydronephrosis. By M. J. Farr, D. W. W. Newling and C. Raper 286

CASE REPORTS—*continued*

PAGE

Antisperm Antibodies in a Case of Secondary Unilateral Testicular Atrophy. By C. LAURENTI, A. FAGIOLI, A. LENZI and F. DONDERO 352
Inversion of the Urinary Bladder. By A. S. THAVARASAH and L. S. ATTYGALLE 353
Absent Dartos. By AHMED SHAFIK 354
Leukoplakia of the Penis—Bleomycin Treatment. By R. SAKODA, M. OKA and K. NAKASHIMA 355
Exstrophy-Variant of the Bladder. By K. KAYE 356
Both Ureteric Orifices on the Same Side of the Bladder. By A. M. K. RICKWOOD 357
Prostatic Adenocarcinoma with Ectopic ACTH Production. By E. A. MOLLAND 358
Renogastric Fistula. By M. A. P. MILLING and G. J. SANTER 423
Neoplasms of Tunica Vaginalis. By A. P. SINHA 424
Urethral Syndrome Associated with Chlamydial Infection of the Urethra and Cervix. By I. ANNE TAIT, ELISABETH REES and R. M. JAMESON 425
Fracture of the Penis. By D. M. DAVIES and I. MITCHELL 426
A Case of Ureteral Diverticula. By H. A. DE CARVALHO 427
Torsion of the Mesorchium—the Testis Twisted upon the Epididymis. By M. OKA, K. NAKASHIMA and R. SAKODA 428
Spermatic Cord Liposarcoma. By K. SENOH, Y. OSADA and J. KAWACHI 429
An Isolated Injury of Right Renal Artery Due to Blunt Trauma. By CHARLES ATIMOMO 430

BOOK REVIEWS 57, 287, 359, 431

BOOKS RECEIVED 57

CONFERENCES AND COURSES 62, 144, 288, 360, 352

CURRENT UROLOGICAL LITERATURE: SELECT BIBLIOGRAPHY i, xvii, xxxiii

POINTS OF TECHNIQUE

An Instrument for Intrarenal Irrigation. By BRUCE S. PEARSON 55
Method of Mobilising the Adherent Obstructed Ureter. By BRUCE S. PEARSON 56

ABSTRACTS OF THE PROCEEDINGS OF THE UROLOGICAL SOCIETY OF AUSTRALASIA, 30TH ANNUAL GENERAL MEETING, PERTH, AUSTRALIA, 1977 63

SUBJECT INDEX

Absent dartos, 354
Abstracts of the Proceedings of the Urological Society of Australasia, 30th Annual General Meeting, Perth, 1977, 63
ACTH production, ectopic, in prostatic adenocarcinoma, 358
Actinomycosis, primary, of kidney, presenting with renocolic fistula, 140
Adenocarcinoma, prostatic, with ectopic ACTH production, 358
Allopurinol, effect on urinary oxalate excretion in stone formers, 455
Alpha-adrenergic agents, in urinary disorders of proximal urethra, 322, 336
Alphafetoprotein
  and beta-human chorionic gonadotrophin in testicular tumours, 605
  serum, in bilharziasis, 134
ANA. *See* Antinuclear antibody
Androgens, receptor proteins for, in prostatic disease, 567
Aneurysm, abdominal aortic, and ureteric involvement, 313
Anus, imperforate, transient ureteric dilatation in neonates with, 16
Antinuclear antibody, positive, in bilateral renal carcinoma with metastasis in gall bladder, 212
Antisperm antibodies, in secondary unilateral testicular atrophy, 352
Arginine, for infertile men with oligozoospermia, 47
Atrophy, testicular, unilateral, secondary, antisperm antibodies in, 352
Azoospermia
  immunological studies of testicular tissue in, 419
  management of, 595
  obstructive, can follicle stimulating hormone estimation replace testicular biopsy in diagnosis of, 415
  obstructive, respiratory function tests, electron microscopy and results of surgery, 598
  testicular biopsy in, 591

Bacteriuria, with diagnostic catheterisation in women with urinary incontinence, 106
Balloon occlusion, pre-operative, or renal artery, for radical nephrectomy, 153
Beta-human chorionic gonadotrophin, and alpha-fetoprotein in testicular tumours, 605
Bilharziasis, serum alphafetoprotein in, 134
Bilharziasis, urinary, and urolithiasis in the Sudan, 294
Biocarbon, in urinary diversion, 485
Biofeedback
  in treatment of detrusor instability, 250
  in treatment of idiopathic bladder instability, 521
Biopsy
  and cytology in study of bladder cancer, 506
  renal, epsilon-amino-caproic acid to control bleeding after, 8
  testicular, in azoospermia, 591
Bladder
  behaviour during physical activity, 387
  cancer, longitudinal study with cytology and biopsy, 506
  carcinoma, left behind, 139
  carcinoma, radical cystectomy for, 492
  contracture, tuberculous, caecocystoplasty for, 511
  distension, prolonged, for detrusor instability, 243
  dysfunction, neuropathic, outflow obstruction in, neuropathic urethra, 190
  exstrophy, treatment by trigonosigmoidostomy, 90
  exstrophy-variant of, 356
  instability, idiopathic, treated by biofeedback, 521
  instability in women with recurrent cystitis, 524
  lymphoma, with bilateral hydronephosis, chemotherapy, 286
  neck incision, for treatment of retention with overflow in absence of adenoma, 395
  neuropathic, anteromedian (12 o'clock) external urethral sphincterotomy in, 99
  of dog, effect of pelvic nerve stimulation and some drugs on, 398
  parasympathetic nerve supply to, damage after abdominoperineal resection of rectum for carcinoma, 95
  pressure, effect on, of sudden entry of fluid into posterior urethra, 406
  pseudo-obstructed, in enuretic children, 505
  rabbit, induction of cystitis and implantation of tumours in, 502
  rat, induction of cystitis and implantation of tumours in, 502
  rupture of, delayed, 162
  rupture, complication of distension therapy, 529
  stones, ultrasonic lithotriptor for, 255
  surgery, polyglycolic acid versus chromic catgut in, 324
  tumours, non-infiltrating, site of recurrence, 237
  unstable, psychosomatic, assessment of, 246
  unstable, treated with bromocriptine, 169
  ureteric orifices both on same side of, 357
  urinary, cancer, adoptive immunotherapy and radiotherapy in treatment of, 328
  urinary, inversion of, 353
Bleomycin, treatment, of leukoplakia of penis, 355
Bone
  marrow acid phosphatase, significance of, in prostatic carcinoma, 185
  scanning, and plasma phosphatases in carcinoma of prostate, 172
  scanning, in assessment of prostatic carcinoma, 178
  scanning, serial, treatment response in carcinoma of prostate, 555
BOOK RECEIVED
  HADFIELD, J. and HOBSLEY, M., *eds. Current surgical practice,* vol. 1, 1976, 57
BOOK REVIEWS
  AMELAR, R. D., DUBIN, L. and WALSH, P. C. *Male infertility,* 1977, 287
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  BLANDY, J. *Lecture notes on urology.* 2nd edn, 1977, 287
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  HODSON, C. J., *ed. Radiology and the kidney.* (Contributions to nephrology, vol. 5), 1977, 58
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  MAYALL, R. C. and WITTE, M. H., *eds. Progress in lymphology,* 1977, 431
  PHILLIPS, J. M., *ed. Laparoscopy,* 1977, 60
  ROBINSON, H. B., HAWKINS, J. B. and VEREERSTRAETEN, P., *eds. Dialysis, transplantation, nephrology.* Proceedings of the European Dialysis and Transplant Association, vol. 14, 1977, 359
  SMITH, R. B. and SKINNER, D. G., *eds. Complications of urologic surgery,* 1976, 57
  STANTON, S. L., *ed. Female urinary incontinence,* 1977, 61
  STRAUSS, J., *ed. Pediatric nephrology,* Vol. 3, 1976, 60
  TAYLOR, K. J. W. *Atlas of gray scale ultrasonography,* 1978, 359
  ULDALL, R. *Renal nursing,* 2nd edn., 1977, 359
  WILLIAMS, D. INNES and CHISHOLM, G. D., *eds. Scientific foundations of urology,* 2 vols, 1976, 57

BRITISH ASSOCIATION OF UROLOGICAL SURGEONS
  Annual Meeting, Brighton, 1978. Announcement, 144
  Annual Meeting, Bristol, 1979. Announcement, 432
  One-day provincial meeting, Nottingham, 1978, 360, 432
Bromocriptine, in treatment of unstable bladder, 169
Brown and Wickham, method, in measurement and interpretation of urethral pressures, 33
Busulphan, causing haemorrhagic cystitis, 210
C.-E. Alken Prize 1978. Announcement, 288
Cadmium induced changes and methyl cholanthrene in rat prostate, 25
Caecocystoplasty, for tuberculous bladder contracture, results, 511
Calcium
  excretion, urinary, influence of refined carbohydrate on, 459
  stone disease of urinary tract, risk factors, 449
Calculus(i). *See also* Stone
  in renal transplants, 302
  urinary, cytological changes in, 81
  urinary, ultrastructure and pathogenesis of, 12
Cancer
  prostatic, advanced, prednimustine therapy, 29
  urinary bladder, adoptive immunotherapy and radiotherapy in treatment of, 328
Carbohydrate, refined, influence on urinary calcium excretion, 459
Carcinoma
  bladder, left behind, 139
  bladder, radical cystectomy for, 492
  of penis, 275
  of prostate, bone scanning and plasma phosphatases in, 172
  of prostate, scrotal and occult preputial metastases from, 143
  of prostate, serial bone scanning in, 555
  of rectum, abdominoperineal resection for with damage to parasympathetic nerve supply to bladder, 95
  prostatic, bone scanning in assessment of, 178
  prostatic, optimum dosage of oestrogen in, 562
  prostatic, significance of bone marrow acid phosphatase in, 185
  renal, bilateral, with metastasis in gall bladder and positive ANA, 212
  renal, in horseshoe kidney, 142
  renal, metastasis to phalanx of hand, 280
  renal, pre-operative arterial embolisation in, 469
  renal, unusual presentation of, 141
Castleman, angiofollicular hamartoma of, 285
Catgut, chromic, versus polyglycolic acid in bladder surgery, 324
Catheter(s)
  indwelling, management of, 102
  self-retaining, with triple microtip pressure transducer, 353
Catheterisation, diagnostic, and bacteriuria in women with urinary incontinence, 106
Cavernositis, 53
Cerebrovascular disease, transurethral resection of prostate in patients with, 539
Chyluria, 126
Computerised tomography, scanning, and surgery of metastatic teratoma of testis, 609
CT. *See* Computerised tomography
Conduit, colonic, continent with new magnetic stoma seal, 264
Contraceptive research and development, request for informal proposals on, 144, 432
Cordopexy, for undescended testis, 39
Current urological literature, i, xvii, xxxiii
Cyst(s)
  in penis of child, 213
  parameatal urethral, congenital, in male, 340
Cystectomy
  radical, for carcinoma of bladder, 492
  total, early postoperative intravenous nutrition after, 319
  total, review, 488
Cystitis
  haemorrhagic, caused by busulphan, 210
  induction of and implantation of tumours in rat and rabbit bladders, 502
  recurrent, and bladder instability, 524
Cytology, and biopsy in study of bladder cancer, 506

Dartos, absent, 354
Detrusor, instability, biofeedback in treatment, 250
Detrusor, instability, prolonged bladder distension for, 243
Dicynene, in transurethral resection of prostate, 547
Distension therapy, bladder rupture an acceptable complication of, 529
Diuresis, renography, in equivocal urinary tract obstruction, 76
Diverticula, ureteral, 427
EACA. *See* Epsilon-amino-caproic acid
Ectopia testis transversa, 215
Ectopia, transverse testicular, 283
Ectopia vesicae, successful pregnancy after, 281
Edinburgh Urological Festival, 1978. Announcement, 144, 216
Electron microscopy, in obstructive azoospermia, 598

Embolisation, arterial, pre-operative, in renal carcinoma, 469
Endoscopes, report of Standing Committee on Urological Instruments, 361
Endoscopic examination in children, 586
Enterocystoplasty, symptomatic and functional results of, 517
Enuretic children, pseudo-obstructed bladder in, 505
Epididymis
  adenomatoid tumour of, histochemical and ultrastructural study, 121
  sarcoidosis of, 211
  testis twisted upon, 428
Epsilon-amino-caproic acid, to control bleeding after renal biopsy, 8
European Association of Urology. 3rd Congress. Monte Carlo, 1978. Announcement, 144
Fistula(e)
  reno-colic, and primary actinomycosis of kidney, 140
  renogastric, 423
Follicle stimulating hormone estimation, or testicular biopsy in diagnosis of obstructive azoospermia, 415

Gonadotrophin, beta-human chorionic, and alpha-fetoprotein in testicular tumours, 605

Hamartoma, angiofollicular of Castleman, 285
Hydronephrosis, primary pelvic, radiograph measurements and contralateral renal size in, 289
Hypertension, following traumatic renal infarction, 54
Immunotherapy, adoptive, and radiotherapy in treatment of urinary bladder cancer, 328
Impotence, surgical management, using inflatable penile prosthesis, 114
Incontinence, sphincteric, alpha-adrenergic agents in, 332
Injury, urethral, and fractured pelvis, 578
Inosine, clinical results of ischaemic renal surgery, 465
Institute of Urology, University of London, Programme of seminars for 1978/79, 432
International Conference on Urinary Calculi, Perth, W.A., 1979. Announcement. 288, 360, 432
International Congress of Nuclear Medicine and Biology, 2nd, Washington, 1978. Announcement, 216
International Kidney Transplant Course, 1st, Barcelona, 1978. Announcement, 62
International Seminar on Neuromuscular Dysfunction of Upper and Lower Urinary Tracts, Fiuggi, Italy, 1978. Announcement, 144
International Society for Cryosurgery, 144, 288
Intimal tear, cause of transplant failure, 52
Intrarenal, irrigation, instrument for, 55
Intravenous nutrition, early postoperative, after total cystectomy, 319
Irrigation, intrarenal, instrument for, 55
Ischaemia, renal, temporary, techniques used for production of, 371
Ischaemia, warm, perfusion characteristics of preserved canine kidneys and, 1
Ischaemic renal surgery, inosine, 465
Isotopic, renal section scanning, computerised, assessment of, 437

Kidney(s). *See also* Renal
  actinomycosis, primary of, with reno-colic fistula, 140
  bilateral pelvic ectopic, 51
  canine, preserved, and warm ischaemia, perfusion characteristics, 1
  ectopic thoracic, 282
  foreign body migrating to, 209
  horseshoe, renal carcinoma in, 142
  horseshoe, transplantation of, 284
  hydronephotic, renal recovery in, 222
  transplant, influence of wound drainage on infection rate in, 160

Leukoplakia, of penis, bleomycin treatment, 355
Liposarcoma, of spermatic cord, 429
Lithotriptor, ultrasonic, for urethral and bladder stones, 255
Lymphocoeles, in renal transplantation, diagnosis and treatment, 307
Lymphoma, bladder, with bilateral hydronephrosis, chemotherapy, 286

Mesorchium, torsion of, 428
Metastasis(es), scrotal and preputial, from carcinoma of prostate, 143
Methyl cholanthrene, and cadmium induced changes in rat prostate, 25
MST. *See* Mucosal electrosensitivity threshold
Mucosal electrosensitivity threshold in urinary incontinence in women, 262

Natulan, in treatment of Peyronie's disease, 111
Neoplasms, of tunica vaginalis, 424
Nephrectomy, radical, pre-operative balloon occlusion of renal artery for, 153
Nephropathy, and obstructive uropathy, distinction by radioisotope transit times, 433
Nutrition, intravenous, early postoperative, after total cystectomy, 319

Oestrogen, optimum dosage in prostatic carcinoma, 562
Oligozoospermia
  arginine for infertile men with, 47
  immunological studies of testicular tissue in, 419
Orchipexy, in prune belly syndrome, 348
Oxalate, excretion, urinary, in stone formers, effect of allopurinol on, 455

Pain, loin, intermittent, value of provocative and acute urography in, 227
Pelvis, fractured, and urethral injury, 578
Penile prosthesis, inflatable, in management of impotence, 114
Penis
  carcinoma of, 275
  cyst in, of child, 213
  fracture of, 426
  leukoplakia of, bleomycin treatment, 355
Perfusion, characteristics, of preserved canine kidneys subjected to warm ischaemia, 1
Peyronie's disease, procarbazine (Natulan) in treatment of, 111

Phenoxybenzamine in benign prostatic obstruction, double-blind study, 551
Phosphatase(s) plasma, and bone scanning, in carcinoma of prostate, 172
Polyglycolic acid versus chromic catgut in bladder surgery, 324
Prednimustine therapy for advanced prostatic cancer, 29
Pregnancy following ectopia vesicae, 281
Procarbazine (Natulan) in treatment of Peyronie's disease, 111
Program for Applied Research on Fertility Regulation, Northwestern University, Chicago. Request for informal proposals on contraceptive research and development, 144, 432
Prostate
  carcinoma of, bone scanning and plasma phosphatases in, 172
  carcinoma of, scrotal and occult preputial metastases from, 143
  carcinoma, serial bone scanning in, 555
  digital examination of, effect on serum acid phosphatase, 182
  rat, methyl cholanthrene and cadmium induced changes in, 25
  transurethral resection, dicynene in, 547
  transurethral resection, evaluation of results, 542
  transurethral resection of, in patients with cerebrovascular disease, 539
Prostatic
  adenocarcinoma, with ectopic ACTH production, 358
  cancer, advanced, prednimustine therapy, 29
  carcinoma, bone scanning in assessment of, 178
  carcinoma, optimum dosage of oestrogen in, 562
  carcinoma, significance of bone marrow acid phosphatase in, 185
  disease, receptor proteins for androgens in, 567
  hypertrophy, benign, urodynamics in, 20
  obstruction, benign, phenoxybenzamine in, double-blind study, 551
Proteins, receptor, for androgens in prostatic disease, 567
Prune belly syndrome, orchipexy in, 348
Pyelolithotomy coagulum, 298
Pyeloplasty in infants and children, method of postoperative drainage, 217

Radiograph measurements and contralateral renal size in primary pelvic hydronephrosis, 289
Radioisotope transit times, distinguishing between obstructive uropathy and nephropathy, 433
Radiotherapy and adoptive immunotherapy in treatment of urinary bladder cancer, 328
Rectum, abdominoperineal resection of, for carcinoma, damage to parasympathetic nerve supply to bladder after, 95
Reflux
  uretero-ureteric, radioisotope method of assessing, 164
  vesicoureteric, in children, management, 474
  vesicoureteric, surgically treated, follow-up, 479
  vesicoureteric, ureteric reimplantation for, 233
Renal. *See also* Kidney(s)
  artery, pre-operative balloon occlusion of, for radical nephrectomy, 153
  artery, right, injury, due to blunt trauma, 430
  biopsy, epsilon-amino-caproic acid to control bleeding after, 8
  carcinoma, bilateral, with metastasis in gall bladder and positive ANA, 212
  carcinoma, in horseshoe kidney, 142
  carcinoma, metastasis to phalanx of hand, 280
  carcinoma, pre-operative arterial embolisation in, 469
  carcinoma, unusual presentation of, 141
  collar, persistent in human adult male, 157
  growth, following reimplantation of ureters for reflux, 367
  infarction, traumatic, followed by severe hypertension, 54
  ischaemia, temporary, techniques used for production of, 371
  mobility, in women attending a pyelonephritis clinic, 73
  pelvis, functional obstruction of and ureter, histological and electron microscopic study, 145
  recovery, prediction of, in hydronephrotic kidneys, 222
  section scanning, computerised isotopic, assessment of, 437
  size, contralateral, and radiograph measurements in primary pelvic hydronephrosis, 289
  surgery, ischaemic, inosine, 465
  transplantation, lymphocoeles associated with, diagnosis and treatment, 307
  transplantation, uretero-neo-cystostomy in, 378
  transplants, calculi in, 302
  diuresis, in equivocal urinary tract obstruction, 76
Resection
  transurethral of prostate, dicynene in, 547
  transurethral of prostate, evaluation of results, 542
  transurethral of prostate, in patients with cerebrovascular disease, 539
Respiratory function tests in obstructive azoospermia, 598

Sarcoidosis, epididymal, 211
Sarcoma, reticulum cell, with bilateral ureteric obstruction, 136
Scanning, bone, serial, treatment response in carcinoma of prostate, 555
Scanning, CT, and surgery of metastatic teratoma of testis, 609
Scanning Electron Microscopy in Reproduction, Los Angeles, 1978. Workshop. Announcement, 62
Scrotum, lymphatics of, visualisation of, by direct intratissue injection of dye, 205
Serum acid phosphatase, effect of digital examination of prostate on, 182

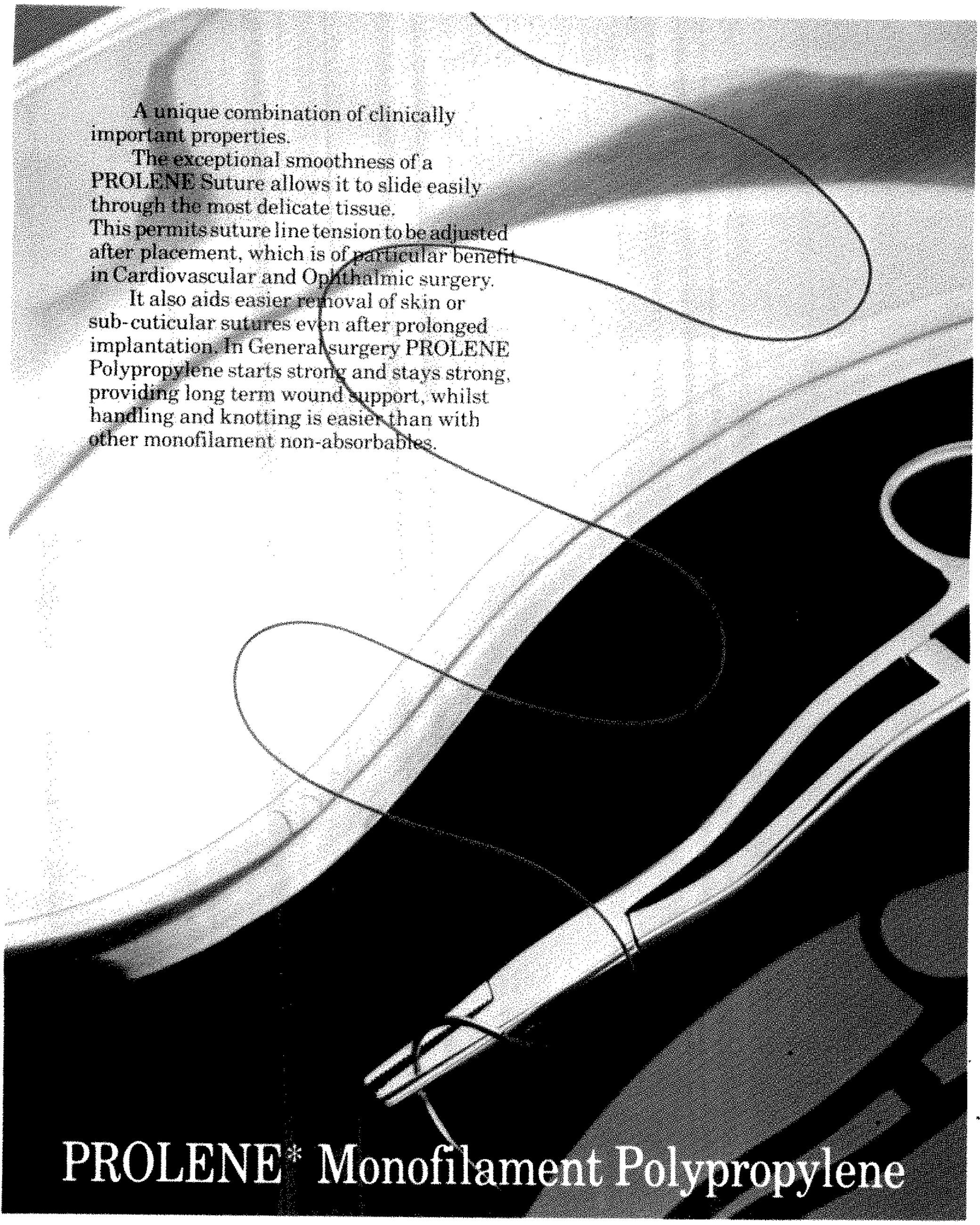
Short Case Reports
  Aaronson, I. A. Carcinoma in the bladder left behind, 139
  Abel, B. J. and Kennedy, J. H. Severe hypertension following traumatic renal infarction, 54
  Ahad, A., Wani, N. A., Bhan, B. L. and Garyali, R. K. Ectopia testis transversa, 215
  Appell, R A., Bagley, D. H., Shield, D. E. and McGuire, E. J. Calyceal injury due to external ureteric compression during urography, 214
  Atimomo, C. An isolated injury of right renal artery due to blunt trauma, 430
  Braf, Z. F. and Horowitz, A. Intimal tear, cause of transplant failure, 52
  Brandina, L., Mocelin, A. J., Fraga, A. M. A. and Lacerda, G. Transplantation of a horseshoe kidney, 284
  Corbett, C. R. An unusual case of cavernositis, 53
  Davies, D. M. and Mitchell, I. Fracture of the penis, 426
  De Carvalho, H. A. A case of ureteral diverticula, 427

Farr, M. J., Newling, D. W. W. and Raper, C. Simple chemotherapy for bladder lymphoma with bilateral hydronephrosis, 286
Fischelovitch, J. and Jancu, J. Bilateral pelvic ectopic kidneys, 51
Heffernan, J. C. and Blenkinsopp, W. K. Epididymal sarcoidosis, 211
Kaye, K. Exstrophy-variant of the bladder, 356
Kennedy, C. L., Williams, G. and Castro, J. E. Angiofollicular hamartoma of Castleman, 285
Khamesra, H. L., Gupta, A. S. and Malpani, N. K. Transverse testicular ectopia, 283
Laurenti, C. and De Dominicis, C. A cyst in the penis of a child, 213
Laurenti, C., Fagioli, A., Lenzi, A. and Dondero, F. Antisperm antibodies in a case of secondary unilateral testicular atrophy, 352
Lome, L. G. Renal carcinoma in a horseshoe kidney, 142
Merimsky, M. and Firstater, M. Ectopic thoracic kidney, 282
Millard, R. J. Busulphan haemorrhagic cystitis, 210
Miller, G. D. and Slade, P. J. B. Successful pregnancy in a patient with previous ectopia vesicae, 281
Milling, M. A. P. and Santer, G. J. Renogastric fistula, 423
Molland, E. A. Prostatic adenocarcinoma with ectopic ACTH production, 358
Oka, M., Nakashima, K. and Sakoda, R. Torsion of the mesorchium—the testis twisted upon the epididymis, 428
Oliveira Filho, J. A. De, Silveira, E. and Marins, J. L. C. Metastasis from renal carcinoma to a phalanx of the hand, 280
Osman, J., Regan, R. J. and Dathan, J. R. E. Bilateral renal carcinoma with metastasis in gall bladder and associated with a strongly positive ANA, 212
Ray, B., Sharifi, R. and Clark, S. S. Massive scrotal and occult preputial metastases from carcinoma of the prostate, 143
Rickwood, A. M. K. Both ureteric orifices on the same side of the bladder, 357
Sakoda, R., Oka, M. and Nakashima, N. Leukoplakia of the penis—bleomycin treatment, 355
Senoh, K., Osada, Y. and Kawachi, J. Spermatic cord liposarcoma, 429
Shafik, A. Absent dartos, 354
Sinha, A. P. Neoplasms of tunica vaginalis, 424
Stack, G. M., Mayo, M. E. and Kiviat, M. D. Foreign body migrating to the kidney, 209
Tait, I. A., Rees, E. and Jameson, R. M. Urethral syndrome associated with chlamydial infection of the urethra and cervix, 425
Thavarasah, A. S. and Attygalle, L. S. Inversion of the urinary bladder, 353
Vandendris, M., Schulman, C. C. and Potvliege, P. Bilateral ureteric obstruction secondary in reticulum cell sarcoma, 136
Ward, A. and Soni, N. An unusual presentation of renal carcinoma, 141
Wesolowski, S. Ureteric stricture after vaginal ureterolithotomy, 137
Wesolowski, S. Ureterosigmoidostomy (Coffey): 30–year follow-up, 138
Yu, H. H. Y., Yim, C. M. and Leong, C. H. Primary actinomycosis of kidney presenting with reno-colic fistula, 140
Society of Uroradiology, 1st Annual Course, New York City, 1978. Announcement, 288, 360
Spermatic cord, liposarcoma of, 429
Standing Committee on Urological Instruments, report, endoscopes, 361
Stimulation, electronic, with mucosal electrosensitivity threshold in urinary incontinence in women, 262
Stoma seal, new magnetic, for colonic conduit, 264
Stomata, pure carbon (biocarbon) in urinary diversion, 485
Stone(s) *See also* Calculus
  "activity", new urinary test for, 442
  disease, calcium, of urinary tract, risk factors, 449
  formers, urinary oxalate excretion in, effect of allopurinol on, 455
Stricture, one-stage excision urethroplasty for, 410
Surgery, results in obstructive azoospermia, 598
Teratoma, metastatic, of testis, CT scanning and surgery, 609
Testicular
  atrophy, unilateral, secondary, antisperm antibodies in, 352
  biopsy, in azoospermia, 591
  biopsy, or follicle stimulating hormone estimation in diagnosis of obstructive azoospermia, 415
  tissue, immunological studies of, in oligozoospermic and azoospermic patients, 419
  tumours, alpha-fetoprotein and beta-human chorionic gonadotrophin in, 605
Testis(es)
  after torsion, 43
  ectopia testis transversa, 215
  teratoma, metastatic of, CT scanning and surgery, 609
  transverse testicular ectopia, 283
  twisted upon epididymis, 428
  undescended, cordopexy for, 39
Transducer pressure, triple microtip, and self-retaining catheter, 535
Transplant failure, due to intimal tear, 52
Transplantation, renal, lymphocoeles associated with, 307
Transplants, renal, calculi in, 302
Transurethral
  resection of prostate, dicynene in, 547
  resection of prostate, evaluation of results, 542
  resection of prostate, in patients with cerebrovascular disease, 539
  surgery, should patients be shaved before?, 109
Trauma, blunt, causing injury to right renal artery, 430
Trigonosigmoidostomy for exstrophy of bladder, 90
Tumour(s)
  adenomatoid, of epididymis, histochemical and ultrastructural study, 121
  bladder, non-infiltrating, site of recurrence, 237
  implantation of and induction of cystitis in rat and rabbit bladders, 502
  testicular, alpha-fetoprotein and beta-human chorionic gonadotrophin in, 605
  urethral, 583
Tunica vaginalis, neoplasms of, 424
Ureter(s)
  functional obstruction of, and renal pelvis, histological and electron microscopic study, 145

  obstructed, adherent, method of mobilising, 56
  reimplantation for reflux, followed by renal growth, 367
  wide, reimplantation of, 383
Ureteral diverticula, 427
Ureteric
  compression, external, during urography, causing calyceal injury, 214
  dilatation, transient, in neonates with imperforate anus, 16
  involvement with abdominal aortic aneurysm, 313
  obstruction, bilateral, secondary to reticulum cell sarcoma, 136
  orifices, both on same side of bladder, 357
  reimplantation, for vesico-ureteric reflux in adult, 233
  stricture, after vaginal ureterolithotomy, 137
Ureterolithotomy, vaginal, followed by ureteric stricture, 137
Uretero-neo-cystostomy in renal transplantation, 378
Ureterosigmoidostomy (Coffey), 138
Uretero-ureteric reflux, radioisotope method of assessing, 164
Urethra
  chlamydial infection of, and urethral syndrome, 425
  neuropathic, 190
  of dog, effect of pelvic nerve stimulation and some drugs on, 398
  posterior, sudden entry of fluid into, effect on bladder pressure, 406
  proximal, alpha-adrenergic agents in urinary disorders of, 332, 336
Urethral
  cyst, congenital parameatal, in male, 340
  injury, and fractured pelvis, 578
  instability, reflex, 200
  obstruction, due to "sympathetic dyssynergia", alpha-adrenergic agents in, 336
  pressures, measurement and interpretation by method of Brown and Wickham, 33
  sphincterotomy, anteromedian (12 o'clock) external, in neuropathic bladders, 99
  stones, ultrasonic lithotriptor for, 255
  strictures, treated by internal urethrotomy and primary split skin grafting, 257
  syndrome and chlamydial infection of urethra and cervix, 425
  tumours, 583
Urethroplasty
  endourethral, 257
  one-stage excision, for stricture, 410
  one-stage island patch, 575
  skin inlay, late results, 570
Urethrotomy, internal, and primary split skin grafting, 257
Urinary
  bilharziasis and urolithiasis in the Sudan, 294
  bladder, inversion of, 353
  bladder cancer, adoptive immunotherapy and radiotherapy in, 328
  calcium excretion, influence of refined carbohydrate on, 459
  calculi, cytological changes in, 81
  calculi, human, ultrastructure and pathogenesis of, 12
  diversion, use of pure carbon stomata (biocarbon) in, 485
  incontinence, diagnostic catheterisation and bacteriuria in women with, 106
  oxalate excretion in stone formers, effect of allopurinol on, 455
  test for stone "activity", 442
  tract, calcium stone disease of, risk factors, 449
  tract, obstruction, equivocal, diuresis renography in, 76
Urodynamic questionnaire, design of, 269
Urodynamics in benign prostatic hypertrophy, 20
Urography, provocative and acute, value, in intermittent loin pain, 227
Urography, with external ureteric compression, causing calyceal injury, 214
Urolithiasis and urinary bilhariasis in the Sudan, 294
Urolithiasis in Sudan, 376
Uropathy, obstructive, and nephropathy, distinction by radioisotope transit times, 433

Varicocele, thermographic characteristics of, 118
Vas, recanalisation of, after vasectomy, techniques in dogs, 342
Vasectomy, recanalisation of vas after, in dogs, 342
Vesicoureteric reflux, in children, management, 474
Vesicoureteric reflux, surgically treated, follow-up, 479
Vulva, lymphatics of, visualisation of, by direct intratissue injection of dye, 205

Wound drainage, influence on infection rate in kidney transplant patients, 160



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J. M. Fitzpatrick, A. R. Constable, T. Sherwood, J. J. Stephenson, G. D. Chisholm and E. P. N. O'Donoghue

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R. Ghanadian, G. Auf, G. D. Chisholm and E. P. N. O'Donoghue

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R. E. Glass, J. T. Flynn, J. B. King and J. P. Blandy

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P. A. Hamilton Stewart, C. K. Anderson, R. E. Williams and P. B. Clark

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M. Dunn, P. J. B. Smith and P. H. Abrams

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J. P. Pryor, K. M. Cameron, W. P. Collins, A. V. Hirsh, J. D. H. Mahony, R. C. B. Pugh and J. M. Fitzpatrick

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M. Sade, Indira Saverymuttu, Olive Dinsdale and J. G. Gow

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